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THE JOHNS HOPKINS HOSPITAL

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January, 1936

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NUTRITIONAL EDEMA IN THE DOG

III. Salt and the Augmentation of Tissue Fluid

A. A. WEECH, M.D., E. GOETTSCH, M.D., and E. B. REEVES

From the Department of Diseases of Children of Columbia University College of Physicians and Surgeons, New York

Received for publication October 22, 1935

In previous contributions (1, 2) the authors have described the progressive depletion in serum albumin and the development of edema which ensue when dogs are maintained on a diet deficient in protein. They have pointed to numerous similarities in behavior between the experimentally induced edema and the dropsy of humans which is associated with malnutrition or with nephrosis. Because in the dog the whole process of development of and recovery from edema can be followed under controlled conditions, it has seemed that the method of obtaining edema in animals should prove useful in the elucidation of obscure features of disease in humans. In the studies to be described in the present paper the comparison between edema in man and in the dog has been extended to include observations on the respective responses to the addition of salt to the diet. The experiments have permitted a more thorough investigation of some aspects of the response in dogs than has been possible heretofore in humans.

It was recognition of the influence of salt in promoting the retention of fluid which induced Widal (3), Strauss (4), and v. Korányi (5) to believe that the cause of dropsy lay in inability of the kidney to excrete the chloride ion. They demonstrated not only that administration of salt led to aggravation of edema in nephritic patients, but also that restriction of salt not infrequently evoked diuresis. Subsequent investigators, while accepting the main concept of renal insufficiency, showed that other sodium salts besides sodium chloride could exert a similar action, whereas potassium or calcium salts did not, and so succeeded in incriminating the sodium rather than the chloride ion. This view of the pathogenesis of edema which places primary blame

on the kidney remained popular for many years and then gradually and with the accumulation of evidence concerning the rôle of extrarenal factors lost the majority of its adherents. At the present time many investigators either ignore or exonerate the kidney as being concerned in the regulation of fluid distribution in the body. The evolution of the modern point of view has been described thoroughly by Peters (6) and by Loeb and his collaborators (7). The latter workers have shown clearly that the response of the nephrotic patient to salt administration can be explained entirely on the basis of low serum protein and without the assumption of renal participation. At the same time they have cited several phenomena which are not consistent with a concept which exonerates all factors other than those concerned in the so-called Starling theory. As a direct consequence of numerous investigations extending over a period of thirty or more years, the facts regarding the behavior of the human being both in health and in disease following the ingestion of salt are known. The pertinent items will be brought out as the description of the findings in dogs proceeds.

The observations to be recorded in this paper may be divided into two parts. Part I will include balance studies in which the intake and output of sodium chloride were followed (a) in a normal dog and (b) in animals during the progressive depletion of the serum albumin which follows maintenance on a diet low in protein. The nature of the response to sudden shifts in the quantity of dietary salt was investigated particularly. Part II will comprise a description of experiments designed to assist in an understanding of the mechanism involved in the retention of fluid which follows salt administration.

METHODS

The composition of the diet, the method of collection of urine and stool during metabolism studies, and the analytical procedure for the determination of nitrogen, have been described previously (1). Sodium was measured in all specimens by Butler and Tuthill's (8) modification of the method of Barbour and Kolthoff. Chloride was determined in urine and in washings from the cage by the Volhard-Arnold method (9) and in stool by the procedure of Van Slyke (10). Specific gravity was estimated in small pyknometer bottles as described by Moore and Van Slyke (11). Plasma volume was measured by the method of Whipple and associates (12) which utilizes vital red dye. Hematocrit estimations were made in capillary tubes as described by Graff and Clarke (13).

PART. I. OBSERVATIONS OF SALT METABOLISM

Protocol 1 (Dog 8–38).—This experiment was planned as a control and designed to show the effect of salt ingestion after a period of salt deprivation in the normal animal. The diet was like that used in other experiments (1) except that 90 grams of the sugar were replaced by the same amount of casein and that the salt mixture was omitted entirely. The intake of sodium chloride was, therefore, limited to the small amounts normally present in the food ingredients. The average of several analyses indicated that this amount was 6.2 millimols of sodium and 8.3 millimols of chloride daily. Distilled water was allowed *ad libitum* for drinking. During the entire experiment, which lasted 77 days, the dog remained in excellent health; the plasma albumin was consistently at a normal concentration above 3.0 grams per 100 cc. From the 43rd to the 49th days inclusive, 500 cc. of distilled water

TABLE I

Metabolism observations with dog 8–38

METABOLISM PERIOD	SODIUM		CHLORIDE		AVERAGE DAILY URINE VOLUME
	Average daily intake	Average daily excretion	Average daily intake	Average daily excretion	
	millimols	*millimols*	*millimols*	*millimols*	*cc.*
1 (6 days)	5.1	7.7	6.8	7.1	297
2 (7 days)	5.2	4.8	6.5	5.0	176
3 (6 days)	6.2	5.0	8.3	2.3	348
4 (6 days)	6.2	8.5	8.3	2.6	192
5 (7 days)	6.2	19.4	8.3	13.8	213
6 (7 days)	6.2	17.6	8.3	13.0	242
7 (7 days)	6.2	6.8	8.3	12.8	633
8 (7 days)	174.7	161.8	176.9	166.6	674
9 (7 days)	177.2	161.9	179.3	171.0	691
10 (7 days)	177.2	165.0	179.3	170.3	629
11 (6 days)	6.2	21.5	8.3	24.2	274

were given daily by gavage to augment the voluntary intake, and from the 50th to the 70th days 10 grams (171.1 millimols) of sodium chloride in 500 cc. of distilled water were administered daily through the stomach tube. During the remaining 6 days of observation no extra salt or fluid was given.

Figures showing the balance of sodium and chloride are presented in Table I; the pertinent period of study is depicted graphically in Chart 1. Although an unexplained rise in the excretion of both electrolytes occurred during the 5th and 6th metabolism periods, the data in general indicate that output followed intake while the dietary salt remained low. Throughout the three periods of high salt feeding, however, intake was regularly higher than excretion. During the last of these, the 10th period, the body weight was practically constant, and it is reasonable to think that the animal must have reached a state of salt equi-

librium during the preceding 14 days of ingestion at the same level. The discrepancy, therefore, between intake and output probably results from technical difficulty in collecting excreta quantitatively from metabolism cages rather than being a true measure of salt retention. Two facts, nevertheless, speak for moderate retention of salt during these periods. In the first place the balance became definitely negative when high salt administration was stopped, and in the second place the weight curve indicates that the body as a whole contained more fluid during the time of high salt feeding than before or after. During the 14 days pre-

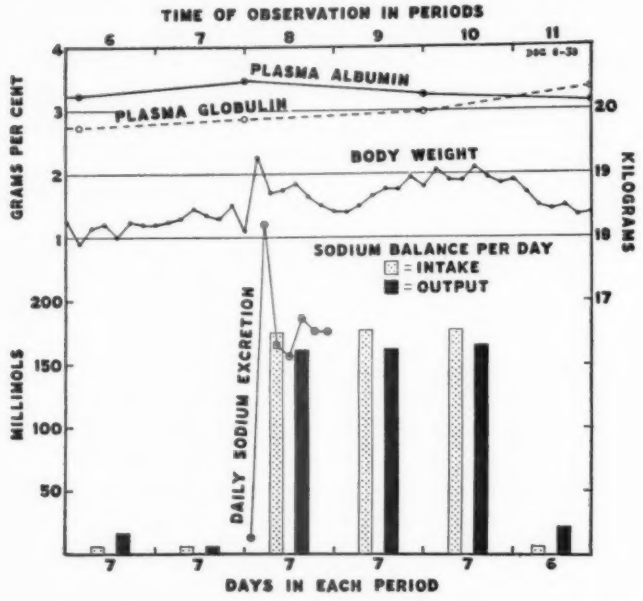

CHART 1. Salt metabolism with dog 8–38. Effect of sudden change in the quantity of ingested salt on a normal animal.

ceding the administration of salt, the average body weight was 18.2 kilos, and during the 21 days of salt feeding the average weight was 18.8 kilos. With discontinuance of the salt the weight declined to approximately its previous value.

In addition to the average daily excretion per period, Chart 1 also shows the actual daily output of sodium during the 7 days following the abrupt change from low-salt to high-salt intake. The output of chloride paralleled that of sodium and is not charted. The first administration of salt was followed by anuria for 24 hours and a gain in weight of 1.2 kilos. During the second 24 hours, there

was a negative sodium balance, and the previous weight increment was partially lost. Thereafter, the daily salt excretion exhibited only minor fluctuations and is, therefore, presented for a single period only.

The salt in this experiment was administered in approximately double physiologic concentration. Although the animal was subsequently allowed to drink as much water as desired, the figures in Table I for urine volume do not indicate that the voluntary intake of fluid was sufficient to bring about physiologic proportions between the intake of water and salt. This is noted specifically because it is known and clearly stated by Peters (6) that the hydropigenous action of salt is most marked when it is administered in a solution of physiologic concentration.

Comment: The reaction recorded in this experiment of the normal dog to salt administration after a period of salt restriction is in harmony with observations which have been made in man. Anuria of 24 hours' duration constitutes an excessive reaction and was probably recorded only because the bladder was not emptied by catheter at the end of the period. It has long been known, however, that there is a definite lag in the excretion of fluid following the administration of salt and water which is not observed when water alone is imbibed (14, 15, 16). Brunn (14), regarding the phenomenon as a matter of general experience remarks, "Denn jedermann weiss, dass auf Suppe nie so profuse Diurese erfolgt, wie auf ein Glas Wasser." The temporary increase in body weight during a period of high dietary salt was known to Widal and Javal (17). The metabolic shifts responsible for the increase are discussed by Peters (6). It appears reasonable to suppose that the greater part of the increase in weight is due to augmentation of fluid in the tissue spaces, although a part of the increase could result from a rise in the volume of the plasma. The deposit of fluid in the tissues is supported by the experience of cattle merchants who know that the tissues of scrawny animals can be filled out to the semblance of good nutrition by administering salt and water shortly before they are driven to market (18). Grüner (19), who performed experiments upon himself, also noted that after the ingestion of salt he had an "auffallend gutes Aussehen."

Protocol 2 (Dog 8–06).—The dog was maintained for 102 days on the protein-deficient diet and exhibited a characteristically progressive decline in the concentration of albumin in the serum. The usual salt mixture was not included in the diet. The balance of sodium and chloride was measured throughout; the

figures for the several periods of study are presented in Table II. The general course of events is shown in Chart 2. The broken line on the chart which is marked "Base Line Weight Curve" requires explanation. It was drawn by subtracting from the animal's initial weight successive decrements calculated from the nitrogen losses which were given in a previous paper (1) for this experiment. The early deviation above this line of the curve of true body weight suggests that some retention of fluid took place even when the diet contained no added salt. Examination of the dog during the latter part of this stage showed that the tissues of the abdominal wall and groin had become full, although there was no palpable edema. After a temporary period of adjustment during the first two periods, equi-

TABLE II

Metabolism observations with dog 8–06

METABOLISM PERIOD	SODIUM		CHLORIDE		AVERAGE DAILY URINE VOLUME
	Average daily intake	Average daily excretion	Average daily intake	Average daily excretion	
	millimols	*millimols*	*millimols*	*millimols*	*cc.*
1 (7 days)	5.9	16.5	4.6	6.4	577
2 (7 days)	5.9	20.6	4.6	10.0	604
3 (7 days)	5.9	7.2	4.6	6.3	595
4 (7 days)	5.9	7.1	4.6	5.1	630
5 (7 days)	5.9	6.6	4.6	5.6	572
6 (7 days)	5.1	5.0	4.0	4.2	473
7 (7 days)	3.2	4.1	2.5	3.1	322
8 (7 days)	2.9	4.3	2.3	3.3	644
9 (7 days)	181.2	176.4	180.6	176.5	970
10 (4 days)	169.0	165.5	85.2	54.6	863
11 (8 days)	2.6	7.9	2.1	7.2	327
12 (4 days)	Break in diet. Observations temporarily discontinued				
13 (7 days)	2.9	7.0	2.3	5.3	1112
14 (7 days)	173.9	115.0	173.3	126.4	1018
15 (4 days)	172.6	87.2	172.2	88.1	724

librium of both sodium and chloride was maintained during the subsequent five periods of low-salt feeding. During the 8th period the dog was given 500 cc. distilled water daily by gavage, and at the beginning of the 9th period the salt intake was abruptly raised by adding 10 gm. salt daily to the gavaged fluid. During the 10th period the high sodium intake was continued, with the difference that half of the sodium was administered as sodium chloride and half as sodium bicarbonate. As in the previous experiment there was a slight positive balance of sodium during the time of high-salt feeding and a subsequent period of slightly negative balance. Again the body weight was maintained at a higher level, but the entire reaction was exceedingly slight and not essentially different from that exhibited by the previous normal animal.

The episode just described may be contrasted with the course of events in the 14th and 15th periods when high-salt feeding was again instituted after the serum albumin had fallen to 1.3 gm. per 100 cc. This time there was a striking retention of sodium and chloride and a corresponding rise in the weight curve. The total gain in weight during these two periods was 3.5 kilos, amounting to 26 per cent of the previous body weight. General anasarca developed. During the last day inanition became extreme and death occurred on the following morning. Autopsy revealed a bronchopneumonia.

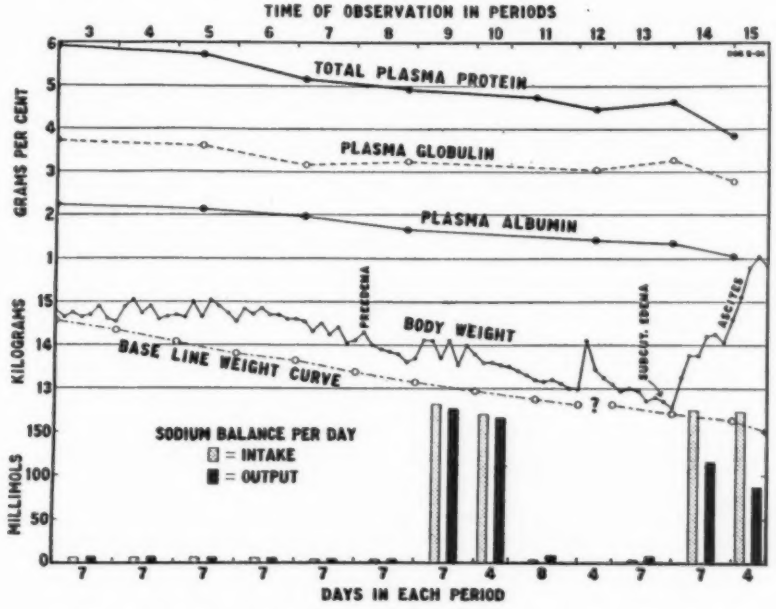

CHART 2. Salt metabolism with dog 8–06. Response to sudden change in dietary salt during progressive depletion of the plasma albumin.

The quantitative aspect of the salt balance during the two periods of retention is presented in Table III. The figures for total excretion of electrolyte were derived from the data in Table II by adding an increment of 6.4 per cent to the measured quantities. The increment represents an attempt to compensate for apparent inability to control completely the collection of excreta; the magnitude of the correction was derived from the measurements during the 10th metabolism period in the previous experiment with a normal dog (*quod vide*). From the

figures for the amount of electrolyte retained we have calculated the gain in weight which would have been expected on the assumption of retention in fluid of physiologic concentration. On the 92nd experimental day, before high-salt feeding was instituted, the serum contained 139.8 m. eq. of sodium per liter and 112.2 m. eq. of chloride. After 5 days of salt feeding the concentrations had risen to 146.0 m. eq. of sodium and 117.7 m. eq. of chloride. A small portion of the retained salt was, therefore, utilized to raise the concentration of extracellular fluid in the body and was not accompanied by a retention of water. By estimating a capacity for the extracellular reservoir of 2.5 liters and by assuming that a proportionate change took place in the concentrations of sodium and chloride in the extravascular reservoirs, the portion of salt diverted for this purpose can be approximated as 16 m. eq. of sodium and 14 m. eq. of chloride. Accordingly these quantities were subtracted from the balance results during the 14th period before calculating the change in weight. It was assumed that further change in concentration did not occur during the subsequent 15th period. Analyses of edema fluid collected on the first day of the 15th period revealed an average

TABLE III

Analysis of observations with dog 8–06 during periods of advance of edema

METABOLISM PERIOD	ELECTROLYTE	TOTAL INTAKE	TOTAL EXCRETION (CORRECTED)	BALANCE	CALCULATED CHANGE IN WEIGHT	OBSERVED CHANGE IN WEIGHT
		millimols	*millimols*	*millimols*	*kg.*	*kg.*
14 (7 days)	Na	1217	856	361	+2.4	+2.1
	Cl	1213	944	269	+2.0	
15 (4 days)	Na	690	371	319	+2.2	+1.3
	Cl	689	375	314	+2.5	

sodium content of 146.4 m. eq. per liter and a chloride content of 125.4 m. eq. per liter. These figures were utilized in the final conversion of retained millimols of electrolyte to calculated gain in weight. A comparison of the calculated and observed gains in weight during the 14th period supports the assumption that electrolyte was retained only along with enough water to produce a solution of physiologic strength. The findings during the 15th period, however, are at variance with this conclusion and suggest an appreciable retention of salt which was not accompanied by water. The significance of this phenomenon is not clear. It may be observed, however, that the dog was extremely weak during this period and by autopsy was shown to have been developing pneumonia.

The feeding of salt in the last two periods of the experiment was associated with a more rapid decline in the total protein level of the serum than had occurred previously. The decline included both the albumin and globulin fractions in such a way that their ratio was not altered. Furthermore, it was attended by a fall in relative red cell volume from 44.1 to 35.9 per cent. The findings suggest an increase in the volume of the plasma.

Comment: In this experiment the administration of salt led to retention and aggravation of edema in a way similar to that which has been observed repeatedly in chronic nephritis. It is reasonable to believe that the response was associated with the deficit of albumin in the serum; and it is therefore of particular interest to note that abnormal retention failed to occur when the albumin concentration was in the neighborhood of 1.6 gm. per cent but did occur subsequently when the level had fallen to 1.3 gm. per cent. During the interim, when the diet did not contain added salt, the dog had developed mild subcutaneous edema. The excessive response to salt feeding may, consequently, be considered to have occurred after the albumin had declined below the "critical level." Shelburne and Egloff (20) have already reported an experiment with a dog similar to this one. They concluded also that the ability to retain large quantities of salt and water was directly related to the serum protein level.

The rise during high-salt feeding in the level of sodium and chloride in the serum is of particular interest. The increase in sodium may be taken as indicative of an increase in the serum total base. Loeb and his associates (7) observed a rise in the total base of serum following the administration of salt to a healthy man, and Albright and Bauer (21) have reported a similar rise in a patient with nephrosis. The latter authors have suggested the possibility of a relationship between elevation of the lowered serum base value toward normal and an increase in total base excretion in the urine. In the present instance the daily excretion of sodium was less during the 15th period than during the 14th period, even though a definite rise had been recorded in the sodium of the serum. Moreover, Loeb (7) has reported large excretions of base in the urine of diabetic patients at times when the serum base was considerably reduced. So, although the available evidence warrants the belief that the level of base in the serum may be one factor in controlling the retention or excretion of base and fluid, there must be additional factors which, being unknown, cannot be evaluated in terms of relative importance.

It has been mentioned that some of the findings with this animal suggest that the volume of the plasma was increased by the administration of salt. This means that both circulation and interstitial reservoir may have participated in the retention of fluid. The

significance of such a possible relationship will be discussed in Part II of this paper.

Protocol 3 (*Dog 8–4a*).—The general plan in this experiment was similar to the preceding one. However, the diet contained the usual salt mixture so that an adequate supply of essential minerals was present throughout. Figures for the salt balance are given in Table IV, and the course of events is outlined graphically in Chart 3. As in the previous experiment, the curve of body weight digresses early from the base line weight curve; during this stage similar physical signs of pre-edema made their appearance. Throughout the first eight metabolism periods (55 days) the ingestion and excretion of sodium and chloride balanced. At the beginning of the 9th period high-salt feeding was instituted and was there-

TABLE IV

Metabolism observations with dog 8–4a

METABOLISM PERIOD	SODIUM		CHLORIDE		AVERAGE DAILY URINE VOLUME
	Average daily intake	Average daily excretion	Average daily intake	Average daily excretion	
	millimols	*millimols*	*millimols*	*millimols*	*cc.*
1 (6 days)	31.6	33.1	34.0	36.2	509
2 (7 days)	31.6	41.2	34.0	41.8	569
3 (6 days)	31.6	27.1	34.0	30.2	624
4 (6 days)	31.6	38.0	34.0	38.0	389
5 (7 days)	26.4	30.6	28.4	29.2	409
6 (7 days)	29.7	32.3	31.9	29.1	414
7 (7 days)	22.2	23.5	24.0	26.2	495
8 (9 days)	23.1	15.8	24.8	21.0	422
9 (3 days)	188.6	181.2	189.4	187.6	967
10 (6 days)	187.7	99.0	188.5	116.1	527
11 (5 days)	183.5	260.9	184.4	248.2	1281
12 (12 days)	175.4	184.2	177.8	184.4	945

after continued at a constant high level for the duration of the experiment. The figures for salt balance and the weight curve both indicate a series of changing responses to the high intake: first, a 3-day period of approximate salt equilibrium associated with a flat weight curve; second, a 6-day period during which much salt was retained and the body weight increased 3 kilos and massive edema appeared; and finally, a 5-day period and a 12-day period during which the balance was negative and associated with diuresis, rapid loss of weight, and subsidence of edema. During the last periods there was no diarrhea, and yet, from the loss of fluid by diuresis alone, the animal's condition changed from anasarca to moderate dehydration. Because her condition had become critical the experiment was terminated. After a short period on a good ration she made an excellent recovery.

The data which portray the quantitative aspect of the salt balance have been

summarized in Table V. The calculations are based on an assumed composition of edema fluid of 145 m. eq. of sodium and 120 m. eq. of chloride. The correction for incomplete collection of excreta was the same as in the last experiment. Because analyses of serum for electrolyte were not made, the computations do not include correction for possible changes in concentration. In this experiment the diet always contained a moderate amount of salt and the intake had been at a

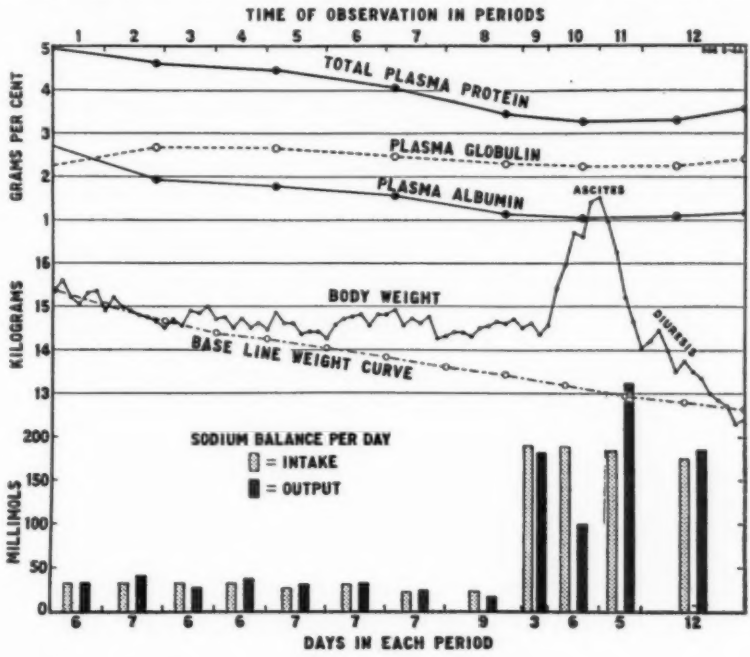

CHART 3. Salt metabolism with dog 8–4a. The experiment reproduces two phenomena which are often observed in human patients: (1) marked retention of fluid following the ingestion of salt, and (2) spontaneous diuresis.

high level for 3 days prior to the periods recorded in the table. For this reason the occurrence of significant changes in concentration in the serum is unlikely. The table discloses satisfactory agreement between calculated and observed change in weight during both the period of retention and the two subsequent periods of diuresis. The findings justify the conclusion that the gains and losses in body electrolyte were the direct result of gains and losses of fluid having the composition of an ultrafiltrate of the plasma.

The data in this experiment also suggest that diuresis was accompanied by a reduction in the volume of the plasma, for the analyses of plasma for protein show that both albumin and globulin rose at this time without change in their ratio. It is improbable that the rise could have resulted from actual protein regeneration.

Comment: In this experiment there have been reproduced two phenomena which are often observed with human patients: (1) marked retention of fluid following the ingestion of salt, and (2) diuresis which could not be attributed to change in the concentration of the protein of the serum. The modus operandi of the retention provoked by salt administration will be discussed later. The reduction in plasma volume during the phase of diuresis means that fluid was removed from the circulation as well as from the tissues, and

TABLE V

Analysis of observations with dog 8–4a during periods of advance and recession of edema

METABOLISM PERIOD	ELECTROLYTE	TOTAL INTAKE	TOTAL EXCRETION (CORRECTED)	BALANCE	CALCULATED CHANGE IN WEIGHT	OBSERVED CHANGE IN WEIGHT
		millimols	*millimols*	*millimols*	*kg.*	*kg.*
10 (6 days)	Na	1126	632	+494	+3.4	+3.0
	Cl	1131	741	+390	+3.3	
11 (5 days)	Na	918	1393	−471	−3.2	−3.4
	Cl	922	1321	−399	−3.3	
12 (12 days)	Na	2105	2352	−247	−1.7	−1.7
	Cl	2134	2354	−220	−1.8	

incriminates the kidney as being primarily responsible for the phenomenon. For if the motivating factor had been one which caused overloaded tissues to discharge their fluid, we should not have expected the circulating blood to give up more than the extra amount of fluid received. The fact that diuresis was uninhibited by a high intake of sodium chloride is of particular interest. S. H. Liu and his associates (22) have observed a similar phenomenon in human subjects with nutritional edema following the administration of sodium bicarbonate. They reported an increase in body weight which reached a maximum within 3 or 4 days and then was followed by diuresis in spite of continued administration of the salt.

Summary of Part I

From observations on the dog recorded in the preceding paragraphs and from findings in man cited from the literature, it may be inferred that canine and human subjects respond in a similar manner to the administration of salt. The features which characterize the response are as follows:

The ingestion of salt and water by healthy subjects after a period of relative deprivation is attended by a lag in the excretion of both salt and water which does not occur when water alone is imbibed. Some hours may be expected to elapse before the mechanism of excretion, presumably a renal factor, begins to operate effectively. Complete elimination and restoration of the previous condition may be delayed for several days, so that if further ingestion at daily intervals takes place, the organism will tend to remain in a state of increased hydration. This fact is indicated by a gain in weight. Cessation of salt ingestion is followed by a negative balance of sodium and chloride and slow return over several days to the previous body mass. In health the magnitude of the weight increment, or hydration increment, is limited, and the maximum attained within a few days, probably often within 24 hours. In conditions associated with a low colloid osmotic pressure of the plasma, the response is similar unless the pressure is low enough to be under the so-called "critical level." When this degree of hypoalbuminemia has been reached, the magnitude and duration of the response to the ingestion of salt and water may be tremendously exaggerated and a previously mild edema may be transformed into general anasarca. The data are not inconsistent with the belief that the retention of salt and water takes place chiefly in the form of a fluid of physiologic concentration.

Spontaneous diuresis with elimination of edema may occur without significant change in the concentration of albumin in the serum. In one experiment described in this paper the findings suggest that the motivating factor in this form of diuresis resides in the kidney. A slight but progressive rise in the concentration of albumin and globulin in the plasma indicated that diuresis had been associated with a decrease in the total plasma volume. In another experiment changes in protein concentration and in relative volume of red cells intimated

that the administration of salt after a period of deprivation produced a moderate increase in the volume of the plasma.

PART II. PHYSIOGENESIS OF THE SALT EFFECT

It is clear from the discussion of the preceding section that an increased ingestion of salt and water generally results in a rise in the store of extracellular fluid in the body. The rise is conspicuous only in the organism which is capable of becoming edematous but is demonstrable also in the normal subject. The evidence suggests that both in normal and in edematous subjects the fluid increment is largely deposited in the tissue spaces, and it follows that the fluid has reached the spaces by passage across the walls of the capillaries. To the student of the Starling theory who believes that the distribution of fluid in the body is controlled by forces operating at the capillary wall, it is desirable to know the effect on these forces of variations in the intake of salt and water. For the moment it is not important that the primary reason for retention may reside at some other point, *i.e.*, in the kidney, and the wanted explanation is not supplied by the statement that edema cannot result unless the body is furnished with the chief solute of edema fluid, *i.e.*, sodium chloride. The fact that a change in the distribution of fluid has occurred compels one to assume some modification in the balance of forces at the capillary wall. It is pertinent, therefore, to inquire directly whether the ingestion of salt and water leads to elevation of the capillary blood pressure, to reduction of the colloid osmotic pressure, or whether additional unknown factors must be sought.

In the experiments to be reported it has not been possible to measure capillary blood pressure, and conclusions regarding change in it must be held in abeyance. Evidence will be presented, however, which suggests that increased ingestion of salt is associated with expansion in the volume of the plasma, and it is not unreasonable to think that the expansion may result in an increment of pressure within the peripheral network of capillaries. Although there is no obligatory relationship between arterial pressure and capillary pressure, it may be noted that Thompson and McQuarrie (23) have observed an increase in general blood pressure following the ingestion of salt. They cite the case of a normal subject who was subsisting on a simple, rela-

tively low potassium diet and in whom the ingestion of 15 grams of sodium chloride every six hours caused an increase in blood pressure from 115/80 to 148/100 mm. Hg.

The thought that plasma volume may be increased by the ingestion of salt is not new. Brunn (14) in 1920 studied the phenomenon by making measurements of the refractive index of serum. His data indicate the development of considerable hydremia four hours after the administration of salt. Because dilution of the plasma implies diminution of its colloid osmotic pressure, this phenomenon has been reinvestigated in the experiments to be described.

Dogs were maintained on the low protein diet without added salt mixture for varying times (from 13 to 47 days) so that different degrees of serum albumin depletion were obtained. Measurements were then made of serum specific gravity, serum protein, relative red cell volume, and total plasma volume. During the next 6 hours the animals received 10 grams of sodium chloride. Half of this amount was mixed with a portion of the diet and fed at once; when this had been consumed the remaining 5 grams were dissolved in 500 cc. water and administered by gavage. The following morning, *i.e.*, about 18 hours after giving the last of the salt, the measurements were repeated. No attempt was made to discover the time at which maximum dilution of the plasma occurred; it seemed more important from the standpoint of physiologic consequences to determine whether a lasting effect could be demonstrated.

Each of the measurement mentioned above permits one to estimate the change in plasma hydration. However, since the errors involved in measuring the several properties are not the same, and because interpretation involves assumptions which cannot be accepted without reservation, the relative value of the different measurements for the purpose of this study requires consideration. The determination of total protein by the Kjeldahl method is most satisfactory. In our experience the probable error of measurement (PE_M) for this substance, when analyses are run in duplicate, is 0.023 gm. per cent.[1] The PE_M of the difference between the consecutive analyses is then 0.033 gm. per cent. Significant altera-

[1] In a previous communication (6) the PE_M for total protein of serum was stated to be 0.054 gm. per 100 cc. This value was not correct. Calculation of the reliability coefficient (r) had been made by the so-called "Short Method" in which the data are grouped into step-intervals. We have since discovered that the Short Method can lead to appreciable error in the PE_M when the value of r is near unity. The value given in this paper was computed without the use of step-interval groupings and is correct within the range of its own probable error, which is ± 0.0014 gm. per cent.

tion in the albumin : globulin ratio during the 24-hour period between samples is unlikely, and a change in the concentration of protein may therefore be interpreted as a change in the colloid osmotic pressure. However, calculation of the magnitude of an increase in plasma volume from a decrease in protein concentration involves the assumption that the total circulating protein has remained constant during the 24 hours. Because the mechanism for replenishing depleted plasma protein is exceedingly labile, the assumption is not entirely justified. Such computations may easily err on the side of giving figures for an increase in plasma volume which are too low. Determinations of serum specific gravity have the same advantages and limitations as those of protein. The dependence of gravity on protein concentration is so close that the former can be used as a measure of the latter (11). The measurement has been included because it can be made with sufficient precision to serve as a check on the nitrogen analyses. All determinations of gravity were made in triplicate. The PE_M in our hands is 0.000078 and the PE_M of the difference between consecutive analyses is 0.000110. The factor 348, calculated from our own data, has been used in converting change in gravity to change in protein. In terms of protein the PE_M of the difference between consecutive gravity readings is, therefore, 0.038 gm. per cent. The error involved in hematocrit estimations is much greater. The figures to be given represent the average of four readings, there being two estimations on each of two blood samples taken by arterial puncture at intervals of about 7 minutes. The PE_M is 0.45 per cent and is greater than when multiple determinations are made from the same blood sample. The PE_M of the difference between the two hematocrit readings before and after salt administration is 0.63 per cent. Furthermore, several considerations may affect the calculation of change in plasma volume from change in hematocrit reading since the assumptions must be made that there is no change in the volume of individual cells and no change in the total number in circulation. If the administration of salt regularly brings about a rise in the total serum electrolyte, there would have to be some compensatory shrinkage in individual red cell volume in order to maintain osmotic equilibrium. For this reason it is possible that the change in plasma volume as calculated from change in hematocrit reading may err on the side of being too large. Finally, the estimation of plasma volume directly cannot be regarded as a precision measurement and there is no practical way of determining the error of measurement. The relative meaning of the several errors of measurement can be expressed clearly in another way. The average plasma volume in the series of dogs studied was 609 cc. With this figure as a starting point, and on the assumption that a small series of experiments may include errors of measurement as great as three times the probable error, the change in plasma volume calculated from protein analyses should be accurate to ± 11 cc., the change computed from gravity determinations should be correct to ± 12 cc., and the change estimated from hematocrit readings should be true within ± 47 cc. The errors expressed in this way are those involved in measurement. They indicate the total error only if one accepts without reservation the assumptions upon which the calculations are based.

Table VI shows for the several experiments the time of maintenance on the low salt diet and the levels of serum protein which had been reached when the effect of salt ingestion was studied. The series does not include animals with edema. In Table VII the values found before and after the administration of salt are recorded. In every

TABLE VI

Experimental conditions obtaining when study of effect of ingestion of salt was undertaken

DOG	TIME ON LOW-SALT, LOW-PROTEIN DIET	INITIAL LEVEL PER 100 CC. SERUM		FINAL LEVEL PER 100 CC. SERUM	
		Total protein	Albumin	Total protein	Albumin
	days	*gm.*	*gm.*	*gm.*	*gm.*
3–87	27	4.87	3.01	3.99	1.83
2–06	47	5.77	3.40	4.68	1.94
3–67b	13	6.73	3.84	5.87	2.69
3–67a*	7	6.27	3.53	6.73	3.84
3–36	21	6.65	3.86	5.35	2.68
2–93	28	5.84	2.94	5.18	2.24

* In this experiment the diet was low in salt only. The addition of casein rendered the diet adequate in protein.

TABLE VII

Findings with the blood of dogs before and about 18 hours after ingestion of 10 grams of salt

DOG	SPECIFIC GRAVITY OF SERUM		PROTEIN PER 100 CC. SERUM		HEMATOCRIT		PLASMA VOLUME	
	Before	After	Before	After	Before	After	Before	After
			gm.	*gm.*	*per cent*	*per cent*	*cc.*	*cc.*
3–87	1.01899	1.01870	3.99	3.92	49.2	46.4	672	632
2–06	1.02105	1.02034	4.68	4.51	37.7	34.8	555	545
3–67b	1.02415	1.02336	5.87	5.73	53.2	50.1	549	701
3–67a	1.02671	1.02540	6.73	6.32	54.7	52.4	610	756
3–36	1.02305	1.02121	5.35	4.88	43.8	38.8	599	656
2–93	1.02180	1.01978	5.18	4.46	49.8	43.4	667	724
Average...	1.02263	1.02147	5.30	4.97	48.1	44.3	609	669

instance a fall in specific gravity, in serum protein, and in relative red cell volume was observed. Direct measurements of plasma volume, however, revealed a slight decrease in two cases and an increase in four cases. For clarity the differences between each pair of measurements are recorded separately in Table VIII. It will be observed

that the order of magnitude of change is roughly the same for gravity, protein, and hematocrit estimations. There are no discrepancies which cannot be explained by the errors of measurement. With plasma volume the order of the differences is irregular when compared with the changes in the other measurements. We believe the irregu-

TABLE VIII

Magnitude of change in blood measurements before and after the ingestion of salt

DOG	SPECIFIC GRAVITY	SERUM PROTEIN	HEMATOCRIT	PLASMA VOLUME
		gm. per cent	*per cent*	*cc.*
3–87	−0.00029	−0.07	−2.8	−40
2–06	−0.00071	−0.17	−2.9	−10
3–67b	−0.00079	−0.14	−3.1	+152
3–67a	−0.00131	−0.41	−2.3	+146
3–36	−0.00184	−0.47	−5.0	+57
2–93	−0.00202	−0.72	−6.4	+57
Average.....	−0.00116	−0.33	−3.8	+60

TABLE IX

Change in plasma volume after ingestion of salt calculated from change (1) in specific gravity of serum, (2) in protein of serum, and (3) in relative red cell volume of blood

DOG	1 FROM SPECIFIC GRAVITY	1 MINUS 2 DIVIDED BY PE_M OF 1 MINUS 2	2 FROM SERUM PROTEIN	3 MINUS 2 DIVIDED BY PE_M OF 3 MINUS 2	3 FROM HEMATOCRIT	AVERAGE OF CALCULATED CHANGES	AVERAGE PER CENT OF INITIAL VOLUME
	cc.		*cc.*		*cc.*	*cc.*	
3–87	+17	0.9	+12	4.2	+80	+36	5.4
2–06	+30	1.5	+21	3.3	+74	+42	7.6
3–67b	+27	2.4	+13	3.7	+73	+38	6.9
3–67a	+44	0.7	+40	1.2	+59	+48	7.9
3–36	+79	3.6	+58	4.9	+137	+91	15.2
2–93	+108	0.0	+108	5.5	+196	+137	20.5
Average....	+50.8	3.4	+42.0	8.5	+103.2	+65	10.6

larity to be caused by the relatively large error in measuring plasma volume. Collectively, the data show definitely that the administration of salt is followed by a decline in serum protein concentration, and the inference is strong that the decline results from an increase in total plasma volume.

If the plasma volume measured before the administration of salt

is accepted as a rough starting point, it is possible to compute the volume increment from the change either in gravity, protein, or hematocrit. The steps involved in this type of calculation have been described in another place (24). Computed changes in volume for the present group of experiments are recorded in Table IX. The volume increments calculated from change in gravity and protein are in good agreement. Although the increments from gravity are regularly in excess of those from protein, the differences between them are small and statistically not significant. However, the volume increments computed from the decline in relative red cell volume are consistently and significantly larger than those calculated from either protein or gravity. Reasons have already been given for suggesting that such increments may be too low when calculated from change in protein concentration and too high when determined from the shift in red cell percentage. It is our belief that the true value for the increment in plasma volume which follows the ingestion of salt lies somewhere between the results obtained by the two methods of calculation. Such values are probably more accurate than can be secured by the methods now available for measuring plasma volume directly. In view of the range of variation it can of course be only accidental that the average of all the calculated changes in volume, 65 cc., agrees so closely with the average of the measured changes, 60 cc.

On the assumption, which is approximately correct, that the average albumin : globulin ratio of the serum in these experiments was 0.9; and by use of the formula of Wells, Youmans, and Miller (25), it can be estimated from the protein analyses that the average decline in colloid osmotic pressure from salt administration was 17 mm. of water and from the gravity determinations that the average decline was 20 mm. of water. It is legitimate to inquire whether pressure changes of this magnitude can affect significantly the distribution of fluid in the body. We have stated elsewhere our belief that during periods of physical inactivity the algebraic sum of forces inside and outside the wall of the capillary must be equal. It follows that even slight change in one of the forces must produce compensatory variation in one or more of the others. A decline in colloid osmotic pressure can be balanced by a fall in capillary blood pressure or by a rise in mechanical pressure outside the capillary. Because a fall in capillary

blood pressure is unlikely, because the evidence presented in Part I of this paper suggests that salt administration increases the volume of fluid in the interstitial spaces, and because such an increase in volume can be expected to augment pressure in the spaces, it appears probable that this latter mechanism is chiefly responsible for establishing the new equilibrium after a decline in osmotic pressure within the capillary. Unfortunately from the quantitative standpoint we do not know that the explanation is adequate. The increase which we believe we have measured in plasma volume may be associated with some rise in capillary blood pressure and thus further augment the force favoring filtration from the capillary. The average magnitude of the volume increase, 60 cc., is approximately 10 per cent of the average original plasma volume and cannot be regarded as insignificant.

Finally, it should be noted (refer to Table VI) that no parallelism was observed between the magnitude of the changes resulting from the administration of salt and the degree of depletion of the serum albumin. The finding permits one to believe that the increment of stress under these circumstances which must be borne by the connective tissue about the interstitial spaces is the same in the normal and hypoproteinemic dog and is in harmony with the concept previously expressed (2), that the major factor in deciding the site and time of appearance of edema is the intrinsic strength of this tissue and not the exact relation between forces operating within the capillary.

DISCUSSION

It remains to discuss briefly the rôle of the kidney in modifying the relatively simple concept of the pathogenesis of edema formation outlined in Part II of this paper and embraced by the Starling theory. It is clear that if the kidney behaved simply as an ultrafilter, a progressive decline in the colloid osmotic pressure of the plasma would be associated with a correspondingly progressive increase in the output of urine. Diuresis arising in this manner might be expected to counteract effectively any tendency toward edema, unless it developed under circumstances wherein a phenomenally large intake of fluid was associated concomitantly with diuresis and with retention within the tissue spaces. Obviously these are not the circumstances which ordinarily attend the formation of edema; deposition of fluid in the

tissue spaces is more commonly associated with diminution in the output of urine. It is outside the scope of this paper to discuss the physiologic factors involved in the excretion of urine by the kidney; nevertheless, it is clear that the kidney is able to and does adjust its excretory mechanism so that diuresis does not result merely because the colloid osmotic pressure of the plasma is low. That is to say, a mechanism exists for the control of urine formation which appears to be independent of those forces which govern filtration and absorption at the peripheral capillary wall. Evidence for such independence of action is easily found. In Part I of this paper it was pointed out that the administration of salt and water is followed by a lag in the excretion of both which is not observed when water alone is given. The excretory lag occurs in the face of changes which favor filtration from the circulation toward the tissue spaces. Furthermore, the sequential occurrence of formation of edema with oliguria and elimination of edema with diuresis (refer to protocol of dog 8–4a) not only exemplifies the same independence of action but suggests that without such independence the usual filtration types of edema could not exist. In the discussion of the findings with dog 8–4a, reasons were presented for the belief that diuresis resulted from a sudden "turning on" of the renal mechanism for excreting salt and water. The finding by no means indicates that all diuresis is initiated in a similar way. In fact, observations by H. J. Stewart (26) indicate that "diuresis, in the presence of heart failure of the congestive type, depends on changes initiated in the tissues, and is accompanied by dilution of the circulating blood." At the present time it is desired merely to emphasize the possibility of diuresis of renal origin. Just how the sudden release of fluid from the circulation through the kidney affects the interplay of forces at the walls of peripheral capillaries is not known. In the experiment with dog 8–4a the slight rise in serum protein concentration seems inadequate to explain the rapid outpouring of fluid from the tissues. It is possible that diuresis of this type may be associated with significant lowering of peripheral capillary blood pressure.

If, then, it is admitted that the kidney, as it functions during diuresis or as it fails to function during the building of edema, is capable ultimately of controlling fluid distribution in the body, it becomes relevant to inquire whether its influence may not vary so continuously as to

relegate to places of minor importance all other factors capable of affecting the forces at the peripheral capillary wall. The facts speak against such continuous variation. The excellent correlations which have been found both in man (11) and in the dog (2, 27) between serum protein levels and edema would otherwise be impossible. During the course of edema the curves for body weight tend to be smooth with periods of gain, plateaus, and periods of loss. Diuresis without change in serum protein is an occasional phenomenon only. And the changes described in this paper following the ingestion of salt have in general been so regular and consistent as to permit one for the moment to relegate the kidney to a subordinate position and focus attention on the peripheral capillary wall.

SUMMARY

Experiments are described in which the intake and output of sodium chloride were followed (a) in a normal dog and (b) in animals during the progressive depletion of the serum albumin which follows maintenance on a diet low in protein. The findings, summarized at the conclusion of Part I of this paper, warrant the inference that canine and human subjects respond in a similar manner to the administration of salt.

Further experiments are described in which an attempt was made to discover why the ingestion of salt and water leads to augmentation of fluid in the interstitial reservoir. When salt is administered after a period of salt deprivation, it is consistently found after a period of about 18 hours that the specific gravity and total protein of the serum and the relative red cell volume of the blood have lower values than initially. Calculation indicates an average decline in the colloid osmotic pressure of the serum of 17 or 20 mm. of water.

The average result of direct measurement of plasma volume suggests that the recorded changes in gravity, protein, and hematocrit result from an increase in the volume of the plasma. Because of the difficulty of measuring plasma volume with accuracy, the individual findings are thought to be devoid of quantitative value, and it is suggested that a better approximation of the magnitude of the increment in plasma volume is obtained by calculations which depend on the changes in protein, gravity, and hematocrit. Such computations indicate an average increase in plasma volume of about 10 per cent.

The possibility is suggested that the increase may be associated with a rise in capillary blood pressure.

A discussion is given of the part played by the kidney in regulating the distribution of fluid in the body and of the rôle of this organ in determining the findings in this and in previous investigations.

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THE INFLUENCE OF INADEQUATE TREATMENT OF EARLY SYPHILIS ON THE INCIDENCE AND INCUBATION PERIOD OF NEUROSYPHILIS[1]

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This study was carried out to test the validity of the assumption that inadequate treatment for early syphilis increases the incidence of neurosyphilis and shortens the interval between infection and the appearance of clinical evidence of neurologic damage. This assumption has been widely accepted, and such careful observers as Keidel (1), Brittingham (2), Langer (3), Spitzer (4), Pette (5), Barnewitz (6), and Massias (7) have inferred or stated that, in so far as the probable development of neurosyphilis is concerned, inadequate treatment for early syphilis is worse than no treatment at all; while Hopkins (8) believes his data to prove the shortening of the incubation period of clinical neurosyphilis by the inadequate treatment of either early or late syphilis. However, his failure to divide his cases according to the stage of the disease at which they were treated, to some extent, invalidates his conclusions. Moore (9), while accepting Hopkins' conclusions as to the influence of inadequate treatment in lessening the incubation period of neurosyphilis, believes that treatment for early syphilis, whether adequate or inadequate, appears to have no influence in increasing the incidence of any form of clinical neurosyphilis, except acute syphilitic meningitis. This, in part, is in agreement with the opinions of Mattauschek and Pilcz (10) during the prearsphenamine era, with the more recent observations of Stokes and DesBrisay (11), and the conclusions of the German Dermatological Association in 1929 (12).

In contrast to the conflicting opinions regarding the rôle of inadequate treatment of early syphilis in the genesis of neurosyphilis, it is

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now agreed that adequate treatment for early syphilis does not increase the incidence of neurosyphilis. The contentions of Scholtz and Willmer (13), Fleischmann (14), and others, that any type of treatment for early syphilis is to be preferred to treatment with arsenicals, even in adequate amounts, are successfully refuted by the studies of the Cooperative Clinical Group (15) which, disregarding the type and amount, showed that approximately 53 per cent of the patients who received treatment for early syphilis experienced an ultimately satisfactory clinical outcome. Although the total number of cases included in individual studies of the rôle of treatment of early syphilis in the production of neurosyphilis exceeds those reported by the Coöperative Clinical Group, the varying treatment standards of each observer make a comprehensive compilations of their results impossible.

In reviewing the literature, one finds three reasons for the assumption that inadequate treatment for early syphilis predisposes to neurosyphilis. They are: (1) The incidence of neuro-recurrences (*i.e.*, acute syphilitic meningitis) is increased in, or almost limited to, patients receiving inadequate treatment for early syphilis (Finger (16), Benario (17), Gennerich (18), Nonne (19), Rothschild (20), Moore (21), Coöperative Clinical Studies (15)). (2) The incidence of asymptomatic neurosyphilis is higher in patients irregularly treated for early syphilis than it is among those who have received regular treatment (Moore and Kemp (22), Weatherby (23)). (3) Studies of groups of neurosyphilitics have always shown that a large percentage received inadequate early treatment (O'Leary (24), Norris (25), Madden (26), Moore (27)).

It seems to us, upon careful analysis, that these observations do not necessarily support the assumption that inadequate treatment for early syphilis increases the incidence of neurosyphilis. In the first place, neuro-recurrences are a precocious type of neurosyphilis. The abrupt, generally severe onset, the bizarre but, within certain limits, almost uniform clinical picture and the prompt response to treatment which occurs in the majority of instances is not seen in any other group of syphilitic neuropathies. This is further confirmed by a pathological picture which, in the few cases that have come to necropsy (28, 29, 30), is distinct from all other types of neurosyphilis. The one exception is the case reported by Lloyd (31) of a patient with an 8th nerve lesion

who, on necropsy, showed a focal lesion of Deiter's nucleus on the right. A solitary gumma of the brain could have produced a similar pathological picture. In addition, the incidence of neuro-recurrences is very small in comparison with the incidence of inadequately treated early syphilis. In the Johns Hopkins Clinic, with a social service department primarily so concerned about the early syphilitic that the fate of many delinquents is known, the percentage of patients who developed neuro-recurrences up to 1929 (21) was only about 2.0 to 3.0 per cent of the total number who had received treatment for early syphilis. Since, in this clinic, a large number of patients who have lapsed from their treatment for early syphilis are ultimately reexamined, this figure probably represents the average incidence of this complication. In this same clinic, the incidence of acute syphilitic meningitis in untreated early syphilis is about 0.3 per cent. Although it appears to be true that inadequate treatment increases the probable incidence of this particular type of neurosyphilis tenfold, it is still unjustifiable to predict a similar effect for other types of neurologic damage. In the second place, it must be remembered that approximately 80 per cent of all patients with early syphilis have central nervous system invasion before treatment is begun (Merritt and Moore (30)), and that regular antisyphilitic treatment abolishes the serologic evidences of early asymptomatic neurosyphilis in a high proportion of cases. It would, therefore, be surprising if patients irregularly treated for early syphilis did not have clinical or asymptomatic neurosyphilis more frequently than those who were regularly treated. It cannot be contended that irregular treatment increases the incidence of neurosyphilis unless it can be shown that the percentage of neurosyphilis is less among patients who received no treatment for early syphilis than it is among those who received inadequate or irregular treatment. Unfortunately, the figures of Bruusgaard (32) are not acceptable for comparison in this connection because of his failure to do routine spinal fluid examinations. However, the experiences of Hoffmann (33) of the Bonn Clinic are acceptable. He found that the percentage of neurosyphilis among patients with untreated early syphilis was only 5 per cent less than it was among those who had received inadequate treatment for early syphilis.

Finally, the fact that any group of neurosyphilitics contains a large

percentage of individuals who were inadequately treated for early syphilis fails to show that the incidence of neurosyphilis was increased by this type of treatment. It does show that inadequate treatment has failed to cure a chronic disease and, since the majority of patients with early syphilis receive inadequate treatment, it is not surprising to find that they comprise a large proportion of any group with late syphilis.

Since practically all the preceding studies have begun with neurosyphilis and the type of treatment received prior to its discovery, it occurred to us to begin with the type of treatment and to determine the incidence of neurosyphilis in each treatment group. Throughout this paper, we use the descriptive terms of "no treatment," "early inadequate treatment," and "early adequate treatment." By "early inadequate treatment," we refer to those patients who, during the course of the first two years following infection with syphilis, received less than twenty injections of one of the trivalent arsenicals and an equivalent number of treatments of a heavy metal, administered during a period of one year. The average amount of treatment for the individuals in this group was eight injections of one of the arsphenamines and eight to twelve injections of one of the heavy metals. Conversely, by "early adequate treatment," we refer to patients who received at least twenty injections of an arsphenamine and twenty injections of a heavy metal within a period of a year, and within two years following the initial infection. While these criteria may appear to be excessive, only twenty cases, included in the group of 226 patients classified as inadequately treated, received as many as fifteen to nineteen injections of each of these two drugs during a year of treatment. In addition to representing a fair medium between the evidently inadequate standards of O'Leary (24) and the very rigid ones of Madden (26), these criteria are in agreement with those of the Coöperative Clinical Group (15) in their study of the results of treatment of early syphilis.

MATERIAL STUDIED

The material studied consists of a review of 1500 consecutive admissions to a large syphilis clinic and utilizes 680 cases in which there was no question about the history of infection, its duration, and the amount of treatment received during the first two years of the infection.

All of them had spinal fluid examinations or had clinical neurosyphilis sufficiently advanced to make this procedure unnecessary for diagnosis. Patients who gave a history of inadequate treatment for early syphilis and who had received desultory treatment for late syphilis were not included unless the diagnosis of neurosyphilis had been established at the time treatment for late syphilis was begun; or unless we felt certain that this late treatment had not influenced the course of the disease. This would seem to give us a more accurate picture of the results of early inadequate treatment and at the same time allow us to utilize our material to the utmost.

Table 1 shows the distribution of cases by sex. This table shows the expected finding that neurosyphilis was more frequent in males than in females.

TABLE 1

Distribution of cases by sex

	TOTAL CASES	NEUROSYPHILIS	NO EVIDENCE OF NEUROSYPHILIS
Males	330	147	183
Females	350	118	232
Total	680	265	415

INFLUENCE OF INADEQUATE TREATMENT OF EARLY SYPHILIS UPON THE INCIDENCE OF NEUROSYPHILIS

In Table 2 is shown the distribution of the cases into various groups classified according to the amount of treatment which they had received. It shows an approximately equal division of the 680 cases between the three classifications of *no*, *inadequate*, and *adequate treatment*. The most striking point shown by the data of this table is that, while 52.6 per cent of those who had had no treatment for early syphilis, showed clinical or laboratory evidence of neurosyphilis, only 43.4 per cent of those who had had inadequate treatment for early syphilis had neurosyphilis. Contrary to expectation, it appears that in this series of cases the incidence of neurosyphilis is not increased by inadequate treatment during the first two years of the disease. Our figures, as a matter of fact, show a decrease in the percentage of

neurosyphilis among the inadequately treated group as compared with those who received no treatment; and the group given early adequate treatment shows a tremendous decrease in the percentage of neurosyphilis. It is our impression that even a much larger series of cases, as strictly delineated as our own, would fail to show that early inadequate treatment increases the incidence of neurosyphilis.

Table 3 shows the distribution of cases according to sex, classified on the basis of the type of treatment received, and the percentage of

TABLE 2

Distribution of cases according to the type of treatment received

	TOTAL CASES	NEUROSYPHILIS	NO EVIDENCE OF NEUROSYPHILIS
No treatment	253	52.6	47.4
Early inadequate treatment	226	43.4	56.6
Adequate treatment	201	16.9	83.1

TABLE 3

Distribution of all cases by percentages in each sex according to the amount of treatment received and the percentage of neurosyphilis in each treatment group

	330 MALES	350 FEMALES
	per cent	*per cent*
No treatment	38.0	36.5
Percentage of neurosyphilis	57.0	50.0
Early inadequate treatment	30.6	35.8
Percentage of neurosyphilis	57.4	32.0
Early adequate treatment	31.4	27.7
Percentage of neurosyphilis	19.2	14.4

neurosyphilis in each treatment group. An interesting feature of this table is the approximately equal division of the three treatment groups between the two sexes and members of the same sex. It is of interest, also, that with no treatment the incidence of neurosyphilis was only slightly higher in males than in females. The most significant point in this table, however, is that neurosyphilis was 25.2 per cent less frequent in females than in males inadequately treated for early syphilis.

That this difference is not due to pregnancy alone (1) is evident from a comparison of the percentages of neurosyphilis in males (57.0) and females (50.0) who received no treatment, and from the fact that pregnancy post-dating infection was approximately as common in the females of all three treatment groups. Whether it may be due to the female's ability to utilize arsenic more fully than the male, either independently of or as a result of pregnancy, is not evident at the present time, nor pertinent to this study. Whatever the reason for the difference, it does not alter the fact that, in this series of cases, in both males and females inadequate treatment for early syphilis did not predispose to neurosyphilis.

INFLUENCE OF EARLY INADEQUATE TREATMENT UPON THE INCUBATION PERIOD OF CLINICAL NEUROSYPHILIS

It seems generally agreed that inadequate treatment for early syphilis shortens the incubation period of clinical neurosyphilis. The various arguments for and against this point of view are very well presented by O'Leary (24), Norris (25) and Moore (9). The last observer, in supporting this contention, quotes freely from Hopkins (8), whose study is not only the most recent, but includes the largest series of cases that has come to our attention. Unfortunately, Hopkins failed to distinguish between the patients who had received inadequate treatment for early syphilis from those who had received inadequate treatment for late syphilis, and in so doing has confused rather than clarified the problem. In addition, he began with patients who had neurosyphilis and then enlarged upon the type of treatment received before the diagnosis had been established.

Of the 680 patients comprising this study, 181 had clinical neurosyphilis, tabes, paresis, taboparesis or late meningovascular neurosyphilis, and in 112 of them it was possible to date the onset of symptoms. The essential data for this group are shown in Table 4.

Although the number of cases is too small to permit definite conclusions, the following points are of interest:

1. The incubation period of clinical neurosyphilis was six years shorter in the group which received early inadequate treatment (11.6 yrs.) than it was in the group which received no treatment (17.6 yrs.). In both males and females of these two treatment groups, the

same difference obtained in favor of those who received no treatment in contrast with those inadequately treated.

2. There was no noteworthy difference in the length of the incubation period in the group which received early inadequate treatment and the one which was adequately treated. This is probably accounted for by our selection of an arbitrary standard of adequate treatment and is not due to any peculiarities within the two groups.

3. In both the patients who received no treatment and those who were inadequately treated for early syphilis, the incubation period of clinical neurosyphilis was longer in males than in females: 19.2 years in the males and 14.9 years in the females of the former group, and 13.1 years in the males in contrast to 8.7 years in the females of the latter group. While it is possible that this difference is due to statistical error resulting from the comparison of a relatively small number

TABLE 4

Duration of incubation period of clinical neurosyphilis

	ENTIRE GROUP	MALES	FEMALES
	years	*years*	*years*
No treatment	17.6	19.2	14.9
Early inadequate treatment	11.6	13.1	8.7
Early adequate treatment	11.4	11.2	11.8

of cases, the uniform difference between the two sexes in both treatment groups suggests some other explanation. This explanation is not apparent at the present. These figures suggest, however, that while females develop neurosyphilis less frequently than males, they are less resistant should infection in the neuraxis become established.

While we are able to confirm Hopkins' contention that early inadequate treatment shortens the incubation period of clinical neurosyphilis, we have as yet no accurate information to support his conclusions that late inadequate treatment brings about identical result.

CONCLUSIONS

In a study of 680 patients, in whom all necessary data are given and of whom 265 had neurosyphilis, we have shown:

1. That early inadequate treatment (given within two years after infection) apparently does not increase the incidence of neurosyphilis; with no treatment, neurosyphilis comprises 52.6 per cent of cases, and with early inadequate treatment it comprises 43.4 per cent of cases.

2. That the incidence of neurosyphilis in males with no or inadequate treatment remains the same; *i.e.*, 57.4 and 57.0 per cent; in females the inadequate treatment group represents 32.2 per cent, and in the group without treatment 50.0 per cent. Thus, in females it appears that early inadequate treatment reduces the incidence of neurosyphilis compared with a group without treatment.

3. That the incubation period of clinical neurosyphilis is reduced approximately five years in a group of early inadequately treated patients as compared with a group receiving no treatment, *i.e.*, from 19.2 to 13.1 years in males and from 14.9 to 8.7 years in females.

4. That the incubation period of neurosyphilis is shorter in females than in males in both treated and untreated groups. The reason for this difference is not apparent from this study.

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PNEUMOTHORAX THERAPY IN LOBAR PNEUMONIA

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INTRODUCTION

Since the report of Friedemann in 1921 (1), a number of papers concerning the employment of artificial pneumothorax in the treatment of lobar pneumonia have appeared. Reports in the foreign literature (2–10), with but few exceptions, have urged the adoption of this form of therapy because of the prompt relief of pleural pain, the apparent decrease in the signs of toxemia, and the production in many cases of an abrupt termination of the disease. It was not until after the experimental work of Lieberman and Leopold (11), and the clinical report of Blake (12), that the procedure was employed to any extent in this country. The former were led to believe, on the basis of their results with experimental pneumonia in dogs, that pneumothorax produced an artificial limitation of the disease similar to the crisis in human pneumococcus pneumonia. In addition, this treatment appeared to have a favorable effect upon bacteremia.

Blake and his associates reported the clinical trial of the method in 22 cases of lobar pneumonia. They pointed out that "artificial pneumothorax, if given early and at sufficiently frequent intervals, with adequate amounts of air to establish rapidly and maintain a slightly positive mean intrapleural pressure, gives promise of being a very valuable procedure in cases of lobar pneumonia without preexisting fibrous pleural adhesions." Their patients without preexisting adhesions were apparently benefited; those with adhesions received no material benefit, while three with late bacteremia died. All but one of these patients were treated before the 5th day of the disease, the majority on the 2nd or 3rd day. Blake materially modified the accepted technique of pneumothorax therapy by demonstrating that amounts of air, up to 1400 cc. at the initial treatment,

and "refills" up to 500 cc. at 4- to 12-hour intervals, could be well tolerated by the patient and, moreover, were necessary for the maintenance of relatively complete collapse of the affected lobe.

Subsequently, numerous reports have appeared in the American literature (13–20). Selection of the cases has varied, and the amounts of air injected have differed widely. The results to date, however, have established certain facts upon which there may be considered to be general agreement.

1. *Selection of cases.* The importance of this factor has frequently been mentioned. Blake has emphasized the selection of early cases with particular regard to the absence of pre-existing fibrous pleural adhesions. Isaacs, Udesky and de Pinto (17) have urged that pneumothorax be restricted to uncomplicated cases of unilateral pneumonia. Other authors have strongly advised against its use in the presence of cardiovascular disease, asthma and advanced emphysema. The experience of Holmes and Randolph (19) has shown that the induction of pneumothorax in children is often a hazardous procedure.

2. *Relief of pleural pain.* Most authors agree that the introduction of even a small amount of air into the pleural cavity separates the inflamed pleural surfaces and thereby lessens pain. With but few exceptions, this has been a striking finding in nearly all of the reported cases.

3. *Relief of toxic manifestations.* Many authors report a prompt lessening of the toxic manifestations following the induction of pneumothorax. These include decrease in cyanosis and dyspnea, and a drop in pulse and respiratory rates. Profuse sweating is also said to occur.

Other factors of a more or less controversial nature stand out:

a. *Amount of air injected.* Blake advocates large initial amounts of air with frequent "refills" in order to produce and maintain a good collapse of the affected lung. Stoll, Hopkins and Martin (20), on the other hand, believe that this procedure has certain dangers, and recommend, as do many others, smaller amounts at less frequent intervals in order to induce only a partial collapse of the affected lobe.

b. *Duration of the disease.* On the basis of his experience with 6

cases, Coghlan (6) believed that the disease was materially shortened, because crisis appeared to follow promptly on the production of pneumothorax, and his conclusions have been endorsed by Holmes and Randolph (19), Moorman (14, 15), and Behrend and Cowper (13). Stoll and his associates more conservatively state that treatment before the third day of the disease results in "detoxication" with fall in temperature and pulse rate, but that treatment after the third day is of little value.

In many of the records of reported cases, certain important data of prognostic value have not been included. The type of pneumococcus causing the infection and the presence or absence of bacteremia have frequently been ignored. That these are extremely important factors in the prognosis of any given case cannot be denied. In addition, there has been frequent disregard of the fact that many cases of pneumonia, particularly those caused by pneumococci formerly classified as Group IV, and even some due to Types I, II and III, often terminate before the average 7–10 day period. In many of the recorded cases the termination of the disease process, occurring at about the same time as in the average untreated case, has been attributed to the pneumothorax treatment. While an apparently dramatic cessation of the patient's illness not infrequently occurred soon after the institution of pneumothorax therapy, there are numerous other records in the literature which, from careful inspection of the charts, showed no appreciable results following this treatment.

In the light of the foregoing observations, it seemed of interest to determine the effect of pneumothorax on a carefully selected group of patients with pneumococcus pneumonia admitted to this hospital early in the course of their disease. The present report includes observations made upon 9 patients, 6 of whom were treated with pneumothorax alone, and in 3 of whom serum was combined with pneumothorax.

METHODS

Selection of cases. Cases for pneumothorax therapy were selected according to the following criteria. The individuals were young adults whose previous general health had been good. The consolidation, as determined by physical and x-ray examinations, was unilateral in

extent and of less than 72 hours' duration. There was no history of existing cardiac disease or asthma. No particular selection of cases according to type of invading pneumococcus was made. Obviously, such a selection included cases from which a favorable result might logically be expected.

Typing. As a routine procedure, pneumococcus typing was performed. With suitable sputum the Neufeld method was usually satisfactory, but occasionally unsuitable specimens caused a delay of 3 to 4 hours until cultures in Avery tubes, or the peritoneal exudate of sputum-injected mice, yielded enough pneumococci for typing.

X-rays. Shortly after admission the patient was moved in bed to the x-ray room, and 2-meter roentgenograms were made of the chest. The exposure was ½ second with 100 milliamperes current. Routinely, an anterior-posterior film was taken with the patient horizontal, and often a second anterior-posterior exposure was made with the patient propped up in bed in the sitting position. Subsequently, frequent films were taken of the chest during both deep inspiration and deep expiration.

Apparatus. A Bethune pneumothorax apparatus was slightly modified by inserting a 3-way stopcock into the lead-off tube, in order to permit determinations of intrapleural pressures bilaterally. A pneumothorax needle connected to a 6-inch length of glass tubing containing a loose plug of absorbent cotton was autoclaved. This was then joined to the non-sterile tubing of the apparatus by means of an adapter. The volume of injected air was readily controlled by a stopcock. Pressures at the end of inspiration and expiration were recorded in terms of centimeters of water.

Technique of injection. The patients were recumbent during treatment. The site of insertion of the needle was the 4th or 5th interspace in the anterior axillary line. After local anesthesia with 1 per cent novocaine, the needle was inserted first into the intrapleural space on the sound or unaffected side. Usually a reading could be obtained immediately, but when the pleural surfaces were lightly adherent, injection of 20 to 50 cc. of air was necessary before a reading was possible. The cavity of the affected side was entered similarly and successive readings of the intrapleural pressures of both sides were recorded. After withdrawal of the needle from the sound side, the

injection of air on the affected side was started. Air was introduced at the rate of approximately 10 cc. per minute, but at times this was increased to 20 or 25 cc. per minute if there were no signs of respiratory or circulatory embarrassment. Air was continuously injected until the mean intrapleural pressure had become zero or slightly positive. Pressure readings, pulse and respiratory rates were recorded at frequent intervals. Blood pressure determinations were made in both arms before and after treatments. Following the technique of Blake, frequent refills were given during the next 48 hours in order to maintain as complete a collapse as possible.

Decompression. In order to facilitate re-expansion of the lung, decompression was performed a short period after the acute symptoms had subsided in every case in which pneumothorax alone had been used. Air was withdrawn from the pleural cavity by means of the Bethune apparatus. By simply fixing the inner cylinder of the apparatus at a reasonable height with the stopcock closed, a partial vacuum was created, and air was withdrawn from the pleural cavity as the column of enclosed liquid fell.

CASE RECORDS

Case 1. J. C., No. 9467. A white male, aged 31, was admitted 9 hours after a typical onset of pneumococcus Type I pneumonia of the right middle lobe. Massive artificial pneumothorax was produced 12½ hours after onset. In the next 17½ hours 2450 cc. of air were injected into the right pleural cavity. This raised the mean intrapleural pressure from 0 to +2.75. The introduction of 3,300 cc. by the 91st hour produced almost complete collapse of the entire right lung, marked shift of the heart and mediastinum to the left, and extensive displacement of the right anterior mediastinal pleura. The disease terminated by crisis on the 5th day. In the next 36 hours 2300 cc. of air were withdrawn from the chest in order to re-expand the right lung. Convalescence was uncomplicated, and the patient was discharged on the 16th day after onset. Chart I indicates his course in the hospital.

X-rays. A. P. horizontal film (Fig. I), 9 hours after onset, showed a soft infiltration of moderate extent in the right middle lobe. Heart and mediastinum were not displaced. A. P. horizontal film (Fig. 2), 21 hours after onset and following the injection of 1550 cc. of air into the right pleural cavity, showed partial retraction of the entire right lung from the chest wall, together with marked increase in density of the shadow in the right middle lobe. Figs. 3 to 6 were taken in different positions 74 hours after onset and following the injection of 3150 cc. of air. Fig. 3, horizontal inspiration, showed marked collapse of the entire right

lung with the exception of the dependent portion, which was suspended slightly by string adhesions; the trachea was in the mid-line, and the heart and mediastinum were slightly displaced to the left. Fig. 4 illustrated the marked change with expiration. There was extensive displacement of the mediastinum and heart to the left; the right mediastinal pleura was far to the left of the mid-line, as was the trachea; there was marked narrowing of the rib spaces, elevation of the left diaphragm and increase in density of the left lung, as a result of diminished aeration. Figs. 5 and 6 showed the results of placing the patient in the sitting position. The collapse of the right lung was even more evident; the upper border of the right upper lobe had descended to the 6th rib posteriorly; the right diaphragm was raised, and the right costophrenic angle was obliterated by a small

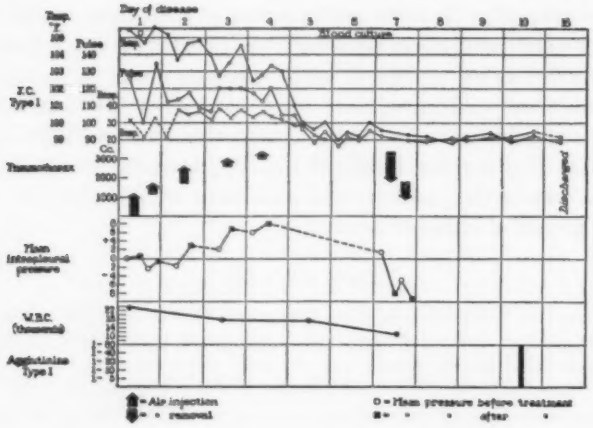

CHART I. Case 1. Pneumococcus Type I lobar pneumonia, treated by artificial pneumothorax.

collection of fluid. The displacement of the mediastinum was not as marked as in the horizontal position. Fluoroscopic examination of the chest at this time, with the patient on a tilting table, demonstrated that the differences in the x-ray appearance of the right upper lobe in the horizontal and sitting postures were due to a gradual displacement of this lobe downwards and forwards. A. P. horizontal inspiration (Fig. 7) and A. P. sitting inspiration (Fig. 8), 6 days after onset and 12 hours after crisis, showed beginning aëration of the right lower lobe, but no change in the extent of the collapse of the lung. The fluid in the right costophrenic angle had increased in amount. A. P. horizontal inspiration (Fig. 9) and A. P. sitting inspiration (Fig. 10), 7 days after onset and 36 hours after crisis, were taken immediately after the removal of 2300 cc. of air. They showed

a striking re-expansion of the entire right lung, with greatest aëration of the right lower lobe. These films gave the impression that the pneumonic process had spread to the right upper lobe while the lung was collapsed. P. A. sitting (Fig. 11) 12 days after onset, showed incomplete resolution of the right middle lobe with moderate pleural adhesions and fluid. P. A. sitting (Fig. 12), 25 days after onset and 9 days after discharge, showed complete resolution.

Comment. Although there was a gradual daily reduction in the height of the temperature during the first four days of the disease, the temperature did not fall below 102.5° until the 5th day. During this time both the pulse and respiratory rates remained constantly elevated. From the 2nd to the 5th day there were definite dyspnea and cyanosis, both of which were markedly increased by each additional "refill." The initial pleural pain was completely relieved after the first 400 cc. of air had been injected. On the following day, however, it was replaced by a steady aching pain somewhat to the left of the sternum, which was increased by each additional injection of air. The x-rays indicated that a probable spread of the consolidation had occurred into the right upper lobe, even though it was collapsed. Crisis on the 5th day in limited Type I pneumococcus pneumonia is not an unusual termination in a relatively young adult, particularly if there is an adequate leucocytic response and bacteremia is not present.

Certain striking changes occurred in the brachial systolic pressures as a result of pneumothorax. These are shown in Table I. As the right intrapleural pressure was raised, the systolic pressure in the right brachial artery gradually increased, while that in the left increased but slightly. When the mean intrapleural pressure exceeded +2.75, systolic pressure was definitely greater during expiration than during inspiration, and this difference was more pronounced on the side of the pneumothorax. Following the withdrawal of air these alterations reverted and the systolic pressures approached the initial levels. Although it has been claimed that pneumothorax should be maintained for some period after the acute symptoms have disappeared (12 and 20), all possible air was withdrawn from the pleural cavity 36 hours after crisis. This procedure permitted an abrupt and almost complete re-expansion of the entire right lung and produced no recrudescence of the disease.

Case 2. B. W., No. 9404. A white female, aged 24, was admitted 16 hours after the typical onset of pneumococcus Type XIX pneumonia of the right upper lobe, and was treated by massive artificial pneumothorax which was begun 19½ hours after onset. 2000 cc. of air injected into the right pleural cavity in the next 6 hours raised the mean intrapleural pressure from −3.5 to +7.0. A total of 2600 cc. of air was injected in the first 68 hours of the disease. This resulted in the production and the maintenance of marked collapse of the entire right lung. The mediastinum was shifted to the left, and the anterior right mediastinal pleura was displaced across the mid-line; this was followed by aching substernal pain. Blood culture, which was positive for pneumococcus Type XIX on admission, remained positive for the first four days of the disease, but at no time exceeded 1 colony per cubic centimeter. Acute otitis media, which developed on

TABLE I

Alteration in systolic blood pressure during pneumothorax therapy, case 1

AIR INJECTED, TOTAL	INTRAPLEURAL PRESSURE, MEAN RIGHT	SYSTOLIC BLOOD PRESSURE					
		Right			Left		
		Exp.	Insp.	Diff.	Exp.	Insp.	Diff.
0	0	124	124	0			
1200	+0.25	124	124	0			
1550	−1.0	112	112	0			
2450	+2.75						
2950	+6.75	140	132	8	112	112	0
3150	+7.5	132	122	10	118	114	4
3300	+6.75	129	120	9	128	120	8
Air withdrawn							
0	+1.0	131	122	9	120	120	0
1500	−7.0	124	120	4			

the 4th day, cleared rapidly after myringotomy. On the day following, a small collection of sterile fluid appeared at the right pleural base and was gradually absorbed. The disease terminated by crisis on the 6th day and convalescence was uneventful. Five days after crisis, 1000 cc. of air were withdrawn from the right pleural cavity. Chart II graphically represents this patient's course.

X-rays. A. P. horizontal (Fig. 13) taken 17 hours after onset showed a soft infiltrating lesion radiating upward and outward into the periphery of the right upper lobe. A. P. horizontal (Fig. 14) 26 hours after onset, following the injection of 2000 cc. of air, showed collapse of the entire right lung and displacement of the mediastinal pleura to the left of the mid-line (line retouched). A. P. horizontal inspiration (Fig. 15) and A. P. sitting inspiration (Fig. 16) 69 hours after onset and after the injection of 2600 cc. of air, showed a maintenance of collapse, and also the characteristic downward displacement of the right upper

lobe when the patient was placed in the sitting position. A. P. sitting inspiration (Fig. 17), 10 days after onset, showed the entire right lung to be still collapsed, but there was beginning aëration of the right upper lobe. P. A. sitting (Fig. 18) 11 days after onset and immediately following the withdrawal of 1000 cc. of air from the right pleural cavity, showed marked re-expansion of the entire lung. P. A. sitting (Fig. 19), 14 days after onset, showed an increased re-expansion of the right lung which was most marked at the base. There was a slight increase in the amount of pleural fluid. P. A. sitting (Fig. 20), 21 days after onset, showed only a small amount of air remaining in the right pleural cavity. There was a slight clouding of the right costophrenic angle.

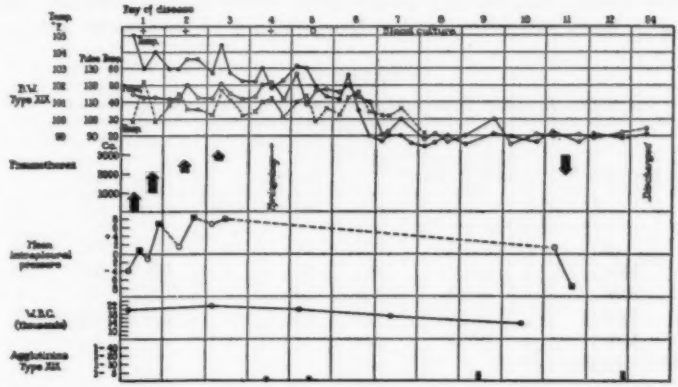

CHART II. Case 2. Pneumococcus Type XIX lobar pneumonia, treated by artificial pneumothorax.

Comment. The temperature, pulse and respiratory rates were not significantly altered as a result of pneumothorax therapy during the first three days of the disease, and the blood culture remained positive during this time. Blood culture was negative for the first time on the 5th day, and on the following day the disease terminated by crisis. Although the initial lesion was relatively small and the collapse was instituted very early in the disease, the only obvious results of pneumothorax were an increase in cough, dyspnea and cyanosis, as well as the production of constant pain to the left of the sternum. Rather definite changes were produced in the blood pressure levels in the two arms as a result of the high right intrapleural pressure. Systolic

pressure increased in both arms, and, simultaneously with the highest intrapleural pressure, was 20 mm. Hg higher in the right brachial artery than in the left. When the intrapleural pressure was greater than +7.0, there was a distinct increase in systolic pressure during expiration as compared with that during inspiration, but this occurred only in the right arm. The data are shown in Table II.

Case 3. A. R., No. 9507. A white male, aged 33, was admitted 16 hours after the onset of pneumococcus Type VIII pneumonia of the right middle lobe. Massive artificial pneumothorax was started 20 hours after onset, and 2000 cc. of air were injected into the right pleural cavity within the next 4 hours. This raised the mean intrapleural pressure from −6 to +1.5, and caused moderate

TABLE II

Alteration in systolic blood pressure during pneumothorax therapy, case 2

AIR INJECTED, TOTAL	INTRAPLEURAL PRESSURE, MEAN RIGHT	SYSTOLIC BLOOD PRESSURE					
		Right			Left		
		Exp.	Insp.	Diff.	Exp.	Insp.	Diff.
0	−3.5	112	112	0	112	112	0
1000	+0.75	112	112	0	108	108	0
2000	+7.0	130	130	0	118	118	0
2500	+8.5	150	148	2	130	130	0
2600	+7.5	146	138	8			
Air withdrawn							
0	+0.5	128	128	0	122	122	0
1000	−7.5	114	114	0	110	110	0

collapse of the entire right lung and slight shift of the mediastinum to the left. After a total of 2500 cc. of air had been injected, pneumothorax therapy was abandoned because spread had occurred to the left lower lobe, and, shortly thereafter, to portions of the left upper lobe. The disease terminated by crisis on the 6th day. Three days later 1300 cc. of air were withdrawn from the right pleural cavity in order to permit re-expansion of the right lung. Convalescence was uncomplicated and rapid. Chart III graphically represents this patient's course.

X-rays. A. P. horizontal (Fig. 21), 17 hours after onset, showed a moderately diffuse soft infiltration of the right middle lobe. A. P. horizontal (Fig. 22), 24 hours after onset and immediately following the injection of 2000 cc. of air, showed collapse of the right lower and middle lobes, but a less complete collapse of the right upper lobe. A. P. horizontal (Fig. 23), 42 hours after onset and following the injection of 2500 cc. of air, showed additional collapse, particularly

of the right upper lobe. There was a significant shift of the heart and mediastinum, although the trachea remained in the mid-line. There was a beginning consolidation of the left lower lobe. A. P. horizontal (Fig. 24), 60 hours after onset, showed an additional spread of the consolidation to involve the entire left lower lobe. A. P. horizontal (Fig. 25), 9 days after onset, and after the withdrawal of 1300 cc. of air from the right pleural cavity, revealed only a small remaining pneumothorax. There was definite clearing of the consolidated lobes. A. P. horizontal (Fig. 26), 14 days after onset, showed almost complete resolution of the pneumonic process.

Comment. Despite an initial single lobar consolidation and the early institution of collapse therapy, the pneumonic process spread

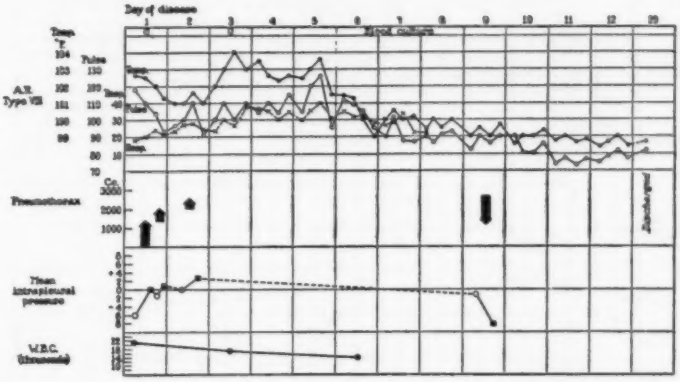

CHART III. Case 3. Pneumococcus Type VIII lobar pneumonia, treated by artificial pneumothorax.

to the opposite lung on the 3rd day. Because of the extensive collapse of the initially affected lung, it was inadvisable to attempt collapse of the contralateral lung; consequently, further pneumothorax therapy was abandoned. The respiratory rate progressively increased from the first day until crisis. No significant differences in the pressures in the brachial arteries were produced by pneumothorax, and the systolic pressures remained similar during inspiration and expiration. It is of interest to note that at no time did intrapleural pressure exceed +2.

Case 4. C. P., No. 9388. A white male, aged 28, was admitted 29 hours after the onset of pneumococcus Type VII pneumonia of the right lower lobe. Massive

artificial pneumothorax was started 32 hours after onset, and within the next 14 hours 2625 cc. of air were injected into the right pleural cavity. This raised the mean intrapleural pressure from −8 to +0.25, produced a marked collapse of all three right lobes and was followed by increased dyspnea, tachypnea, cough and cyanosis. A total of 3025 cc. of air was injected in the first 58 hours after onset. Because of the marked shift of the mediastinum, the displacement of the anterior right mediastinal pleura to the left, and the ensuing distressing symptoms, it was necessary to withdraw 400 cc. of air from the right pleural cavity on the 6th day. On this day sterile fluid appeared in the right pleural cavity and increased so that it was necessary to remove 580 cc. Although the pulse rate reached a normal level on the 6th day, the temperature did not remain normal

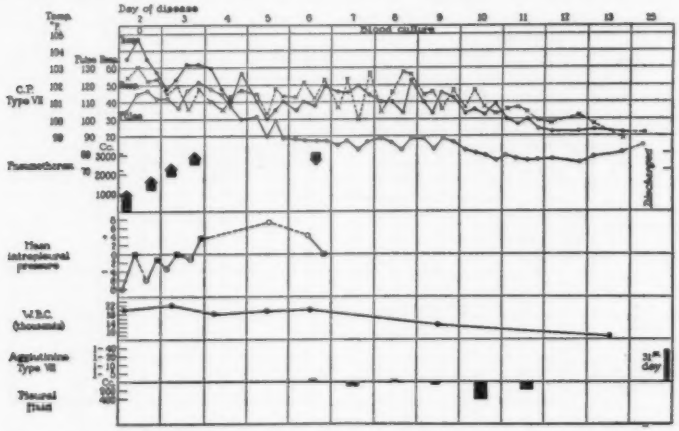

CHART IV. Case 4. Pneumococcus Type VII lobar pneumonia, treated by artificial pneumothorax.

until after the 12th day. The consolidation was gradually resolved, and on discharge on the 25th day almost no evidence of the initial process remained. A small collection of fluid persisted in the right costophrenic angle. The injected air had been completely absorbed. This patient's course is shown in Chart IV.

Comment. The temperature dropped gradually each successive day, and in the middle of the 5th day, simultaneously with the drop in pulse rate, it reached almost a normal level. The secondary rise may be explained on the basis of the developing pleural exudate, even though this remained sterile. In spite of the fall in temperature and pulse rate, respirations remained elevated and irregular. Evidently

the extensive collapse of the right lung did not shorten the pneumonic process materially. Although relief from the initial pleural pain occurred after the introduction of 300 cc. of air, there eventually developed an aching substernal pain. Not only did the pneumothorax fail to relieve the dyspnea, cough, cyanosis and tachypnea, but rather increased all of these manifestations. No significant changes in arterial blood pressure occurred until the mean intrapleural pressure reached +4.5, when the systolic pressure was 10 mm. Hg higher in the right arm during expiration than during inspiration. The systolic pressure levels are shown in Table III.

TABLE III

Alteration in systolic blood pressure during pneumothorax therapy, case 4

AIR INJECTED, TOTAL	INTRAPLEURAL PRESSURE, MEAN RIGHT	SYSTOLIC BLOOD PRESSURE					
		Right			Left		
		Exp.	Insp.	Diff.	Exp.	Insp.	Diff.
0	−7.5	110	110	0			
1200	+1.5	108	106	2	114	114	0
1825	−1.25	118	118	0	110	110	0
2625	+0.25	114	114	0	118	118	0
3025	+4.5	132	122	10	128	122	6
Air withdrawn							
0	+4.0	118	118	0	104	104	0
400	0.0	114	114	0			

Case 5. H. G., No. 9503. A white male, aged 24, was admitted 48 hours after the onset of a pneumococcus Type XX pneumonia of the right lower lobe. Massive artificial pneumothorax was instituted 50 hours after the onset of the disease. 1800 cc. of air injected into the right pleural cavity in the next 6 hours raised the mean intrapleural pressure from −6.5 to +1. 2200 cc. injected between the 50th and 71st hours resulted in marked collapse of the entire right lung, a definite shift of the mediastinum to the left, and displacement of the anterior right mediastinal pleura across the mid-line. Crisis occurred on the 6th day, and 24 hours later 800 cc. of air were withdrawn from the right chest in order to permit reexpansion of the lung. Convalescence was uninterrupted, despite the collection of a small amount of sterile fluid in the right costophrenic angle. On discharge, 17 days after onset, there were no remaining evidences of the previous consolidation, and only a minimal residual pneumothorax. Chart V represents the course.

Comment. The course of this patient's infection was mild, and it was only on the 4th day, after 2200 cc. of air had been injected, that

the temperature reached 103°F. An extensive collapse was secured by pneumothorax. The initial pleural pain was relieved by the first pneumothorax and no subsequent thoracic pain developed. No significant therapeutic results were demonstrable, and the disease process ended on the 6th day. Alteration in systolic blood pressure was not marked, but at the time that the mean intrapleural pressure was highest on the right (+1.0) the pressure in the right brachial artery exceeded that in the left by 14 mm. Hg. There were no differences between pressures taken during expiration and inspiration. A marked bradycardia, which was first noted during convalescence, was shown by adequate tests to be physiological for the patient.

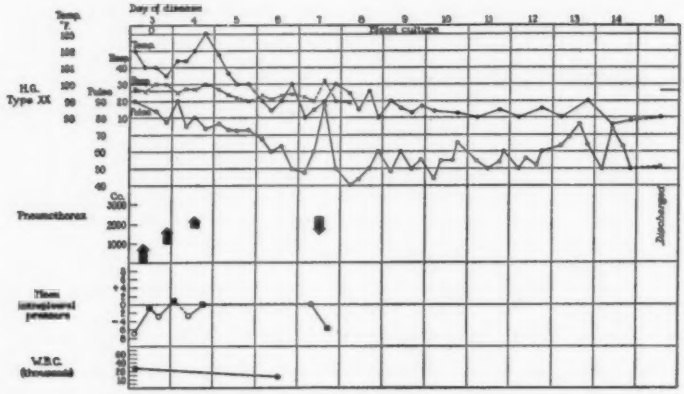

CHART V. Case 5. Pneumococcus Type XX lobar pneumonia, treated by artificial pneumothorax.

Case 6. M. B., No. 9483. A white female, aged 37, was admitted 48 hours after the onset of pneumococcus Type VIII pneumonia of the right middle lobe. Massive artificial pneumothorax was begun 51 hours after the disease started. 1600 cc. of air injected into the right pleural cavity within the next 6 hours, raised the mean intrapleural pressure from −7 to +5.5. A total of 2450 cc. of air was injected during the first four days and caused marked collapse of all three right lobes, moderate shift of the mediastinum to the left, and displacement of the right mediastinal pleura to the left of the mid-line. There was a definite and considerable increase in both cyanosis and dyspnea following the injections of air. The disease terminated by crisis on the 6th day, and 36 hours later 1500 cc. of air were withdrawn from the right pleural cavity to facilitate re-expansion of the

lung. Uncomplicated recovery occurred. Seventeen days after onset the evidences both of the consolidation and the pneumothorax had almost disappeared. Chart VI is a graphic representation of this patient's course.

Comment. Temperature and pulse varied markedly during the first five days of the disease, and neither remained normal until after the crisis on the 6th day. The relatively inelastic chest showed definite evidence of emphysema. The high positive intrapleural pressures, as well as the marked increase in dyspnea and cyanosis, were probably a direct result of this abnormality, and demonstrated the difficulties of extensive collapse in such a chest. The initial pleural

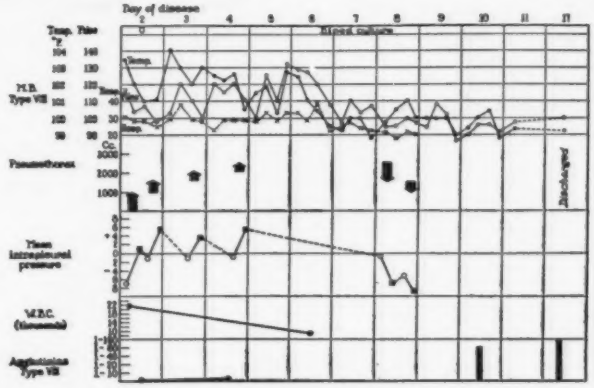

CHART VI. Case 6. Pneumococcus Type VIII lobar pneumonia, treated by artificial pneumothorax.

pain which was relieved by the first air introduced was later supplanted by a sensation of tightness and finally by persistent retrosternal pain. Marked changes in the systolic pressure in the right brachial artery, which were dependent upon the phases of respiration, were associated with the high right intrapleural pressures. At one time, when the mean intrapleural pressure was +5.5, the systolic pressure in the right brachial was 26 mm. Hg higher during expiration than during inspiration. These alterations are shown in Table IV.

Case 7. H. F., No. 9515. A white female, aged 19, was admitted 9 hours after the typical onset of Type II pneumococcus pneumonia of the left lower lobe

and treated with New York State Type II concentrated antipneumococcus serum intravenously.[1] A total of 90 cc. was injected in three doses of 30 cc. each between the 17th and 26th hours after onset, and an additional 60 cc. in two doses between the 41st and 45th hours after onset. A small left artificial pneumothorax was established 12 hours after onset of the disease, by the injection of 450 cc. of air, in an effort to relieve the severe pleural pain. The disease terminated by crisis on the 3rd day. Convalescence was uneventful except for moderate serum sickness and a small collection of sterile fluid in the left costophrenic angle.

Comment. The severe pleural pain was completely and permanently relieved by the small pneumothorax. The collapse produced was minimal and amounted to no more than a separation of the pleural surfaces. This was most evident over the left upper lobe where it measured only 1 cm. At the beginning of serum treatment the

TABLE IV

Alterations in systolic blood pressure during pneumothorax therapy, case 6

AIR INJECTED, TOTAL	INTRAPLEURAL PRESSURE, MEAN RIGHT	SYSTOLIC BLOOD PRESSURE		
		Right		
		Exp.	Insp.	Diff.
0	−7.0	124	124	0
1000	+1.0	124	122	2
1600	+5.5	132	128	4
2450	+5.5	148	122	26
Air withdrawn				
0	−1.0	138	124	14
1500	−7.75	124	118	6

temperature was 105.8°, and pulse and respiratory rates were correspondingly elevated. Twelve hours after beginning serum therapy, temperature, pulse and respiratory rates were normal, but in the following 8 hours a secondary rise in temperature occurred which was controlled by additional serum. Temperature, pulse and respiratory rates became normal at the end of the 3rd day after onset and remained so throughout convalescence except for the rise associated with serum disease.

Case 8. E. L., No. 9375. A white male, aged 17, was admitted 36 hours after onset of mixed Type I and Type XXII pneumococcus pneumonia of the left

[1] This serum was obtained through the courtesy of Dr. Augustus B. Wadsworth.

lower lobe, and was treated by a small artificial pneumothorax induced 50 hours after onset. A total of 650 cc. of air injected into the left pleural cavity raised the mean intrapleural pressure from −8.5 to 0, and produced only a moderate collapse of the left lung. It apparently did not alter the pneumonic process, although the initial pleural pain was completely relieved. Because of the lack of improvement, 30 cc. of concentrated Type I antipneumococcus serum were given intravenously in divided doses on the 5th day. A severe reaction interrupted serum therapy, but crisis occurred on the following day. Except for a collection of sterile fluid in the left pleural cavity, 150 cc. of which were withdrawn, and a mild serum sickness, convalescence was uninterrupted. At the time of discharge

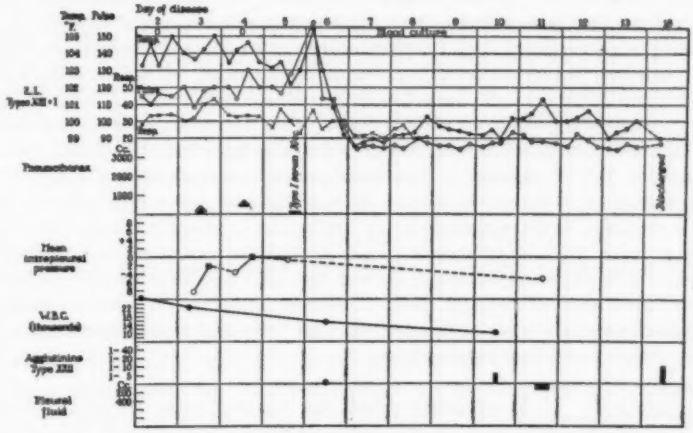

CHART VII. Case 8. Pneumococcus Type XXII, and Type I, lobar pneumonia, treated by artificial pneumothorax and Type I serum.

on the 24th day the fluid had been almost entirely reabsorbed, the lung was nearly re-expanded, and evidence of consolidation had disappeared. The course is shown in Chart VII.

Comment. Pneumothorax, although small in extent and begun relatively late in the disease, completely relieved pleural pain, but had no appreciable effect upon the course of the disease up to the time that serum therapy was instituted. Intrapleural pressures initially were almost identical on the two sides (left, mean −8.5, right, mean −8.0). Although the mean intrapleural pressure on the left was raised to 0

by the injection of air, the mean pressure on the right was raised only to −5.5. What part of the striking effect following the small dose of serum was specific, and what part was non-specific and due to the severe reaction, it is impossible to state.

Case 9. F. C., No. 9464. A white male, aged 43, was admitted 70 hours after onset of Type I pneumococcus pneumonia of the right upper lobe, and was treated by artificial pneumothorax which was begun 72 hours after the onset. A total of 1200 cc. of air was injected into the right pleural cavity within the next 8 hours. This raised the mean intrapleural pressure from −2 to +7 and caused marked collapse of the entire right lung, but was followed by increased dyspnea and cyanosis. When the initial blood culture was found to be positive for Type I Pneumococcus, concentrated Type I antipneumococcus serum was given intravenously. Not only was further pneumothorax therapy discontinued, but 860 cc. of air were withdrawn from the right pleural cavity to relieve symptoms. A total of 200 cc. of serum was given in six divided doses. Thirty-six hours after the beginning of serum therapy, and simultaneously with the development of a positive skin test with Type I capsular polysaccharide, temperature, pulse and respiratory rates dropped to normal by crisis. On the following day a small collection of fluid developed in the right costophrenic angle and was associated with an irregular rise in fever of two days' duration. On the 10th day serum sickness appeared. On the 17th day roentgenograms showed that there had been a sudden increase in the air content of the right chest. This may have resulted from the spontaneous rupture of a small emphysematous bleb. On discharge 4 days later there was almost no residual pneumothorax.

Comment. It is probable that the marked rise in intrapleural pressure following upon the injection of 1200 cc. of air was due to the rigidity of the thoracic cage and the inelasticity of its contents. Physical and X-ray examinations had shown definite evidence of emphysema, and the spontaneous pneumothorax which developed late in the course of the disease may have been due to the rupture of a peripheral pulmonary bleb. Because of the positive blood culture, together with symptoms resulting from pneumothorax, serum was given.

DISCUSSION

Volume of injected air. In this small series of cases there were six patients who received large amounts of air within short periods in an effort to collapse the affected lung as completely and as rapidly as

possible. The remaining three patients were given small amounts of air, largely for the relief of intractable pleural pain. The latter also received type-specific antipneumococcus serum. The technique suggested by Blake was followed in accordance with the theory that only by collapsing the lung to a marked degree could one obtain immobilization of an extent sufficient to modify the disease materially. In the first six cases the average total volume of air injected was 2679 cc., the smallest amount 2200 cc. and the greatest amount 3300 cc. That it was possible to inject such large amounts of air was due to the fact that the majority of the patients were healthy young adult males with large thoracic cages. In these patients the flexibility of the thorax and its contents was such as to permit the introduction of relatively large amounts of air with but a gradual increase in intrapleural pressure. In the three cases in which pneumothorax was combined with serum therapy, the average amount of air injected totalled 766 cc. In two patients (Cases 6 and 9) a considerable degree of emphysema was present, and mobility of the thorax was definitely limited. In the presence of this condition small amounts of air were found to produce rapid rises in intrapleural pressure which resulted in marked respiratory distress. The thoracic mechanics in emphysema has been studied extensively by Christie (21), who emphasizes the inadvisability of inducing pneumothorax in this condition.

Intrapleural pressure. Determination of the intrapleural pressure on the affected side was made in each of the 9 cases before treatment was begun and at frequent intervals during the course of each injection. In addition, simultaneous determinations of the initial intrapleural pressure on the unaffected side were made in all except one case. In three of these 8 cases a number of readings were made on the unaffected side during the course of therapy. On the affected side the lowest initial mean pressure was -8.5 cm. of water, and the highest zero. On the unaffected side the lowest initial mean pressure was -8.0 and the highest $+1.5$ cm. Comparison of the simultaneous observations of the initial mean pressure on the two sides of the chest revealed a close parallelism between the figures in each case. The results show an average difference between the affected and unaffected sides of only 2 to 3 cm. of water. In the three cases in which more than one reading on the unaffected side were taken, a relatively slight

increase in mean pressure occurred (average—3 cm. of water), despite the considerable increase in intrapleural pressure on the affected side (average—10 cm.). The observations of Blake upon the influence of postural changes on the intrapleural pressures were confirmed.

X-ray changes. Extensive collapse of the affected lung was demonstrated by X-ray in all six patients treated with large amounts of air. Small adhesions encountered only twice in this series were not sufficient to prevent collapse. A marked displacement of the heart and mediastinum was not unexpected. The almost constant finding of marked displacement of the anterior mediastinal pleura, when intrapleural pressures were highest, is of unusual interest. In long continued pneumothorax therapy, in which relatively high pressures are maintained, as in certain cases of pulmonary tuberculosis, a somewhat similar stretching of the parietal pleura is not infrequent and may even assume proportions sufficiently great to warrant the designation "pleural hernia." Attention has not previously been directed, however, to this complication of very rapidly induced pneumothoraces in lobar pneumonia. X-rays in Cases 1 and 2 (Figs. 4 and 14) show the extent of the mediastinal and pleural displacement (photographs retouched).

Other findings of interest, and those which should be considered in the interpretations of x-ray films in the pneumothorax therapy of pneumonia, are the alterations that take place in the appearance of the lung during various phases of respiration and also with changes of the patient's position. Figures 3 to 6, Case 1, show a remarkable change in the position of the right upper lobe, brought about by displacement of that lobe downward and forward and best visualized under the fluoroscope. Attention has been called by Stoll and his coworkers to the general haziness of the contralateral lung following the introduction of large amounts of air. This is well seen in Figures 4 and 6, in films taken at the end of a deep expiration. Whether this represents diminished aeration through partial collapse of the unaffected lung, or vascular congestion, is not clear. Another noteworthy point is that following the removal of large amounts of air from the chest, with consequent re-expansion of the lung, evidence may be found that spread of the pneumonic consolidation has taken place within the collapsed lung (Case 1, Figs. 9 and 10.)

Changes in systolic blood pressure. By frequent observations of the blood pressure throughout the course of pneumothorax therapy, it was found that marked changes often occurred in the arterial pressure of the arm on the side of the lesion. The systolic pressure on the affected side increased correspondingly with the rise in intrapleural pressure. Moreover, the pressure on the affected side frequently became paradoxical, and was considerably higher during expiration than during inspiration. The extent of the increase during expiration paralleled the height of intrapleural pressure. When the paradoxical nature of the blood pressure was greatest, similar variations were often detected in the quality of the pulse. Less significant changes were observed in the character of the blood pressure on the unaffected side. The explanation of these phenomena is not yet understood.

Relief of pleural pain. This was the most striking therapeutic result observed in every case in which pleural pain was a presenting symptom. Complete relief occurred in all 7 cases. It was prompt and usually occurred following the injection of only a few hundred cubic centimeters of air. However, pleural pain of a different character, as previously mentioned, sometimes was associated with the relatively rapid change in the position of the mediastinum and the rapid stretching of the mediastinal pleura. In most instances this continuous dull retrosternal pain was more annoying than the original sharp intermittent pleural pain.

Relief of toxic manifestations. In contrast to most of the case reports in the literature, a reduction in the signs of toxicity was not observed in this series. While no determinations of oxygen saturation were made, it was our impression that cyanosis was not relieved, but in most cases was actually increased. While sweating frequently followed the institution of pneumothorax, there was no accompanying feeling of well being on the part of the patients. Inspection of the charts shows no abrupt and sustained fall in the temperature or pulse rates. The respiratory rate in most instances not only failed to decrease, but often was increased (Case 4). Dyspnea was accentuated rather than relieved.

Effect upon duration of disease. Of the six cases given pneumothorax alone, in three treatment was begun on the first day of the disease, in two on the second day, and in one on the third. The acute

disease terminated in one case on the fifth day (Case 1), and in four cases on the sixth (Cases 2, 3, 5, 6). In one patient (Case 4), despite a drop in temperature and pulse rate on the fifth day, acute symptoms persisted until the twelfth day and during this week a large collection of pleural fluid was present. Thus, in this small series, despite very early treatment and relatively complete collapse of the affected lung, there was little or no evidence that the therapy materially shortened the duration of the disease.

Complications. In five of the nine cases included in this report an abnormal amount of pleural fluid was detected, but in only two was there sufficient exudate to require aspiration (Cases 4 and 8). Empyema did not develop. The frequency with which pleural fluid accompanies pneumothorax has been commented upon by other authors (Holmes and Randolph, Stoll, Hopkins and Martin).

Bacteremia occurred in only two of the nine cases. In one of these (Case 9) the blood became sterile after Type I serum therapy. In the other (Case 2) pneumococcus Type XIX bacteremia persisted for four days, during which time pneumothorax treatments were given at frequent intervals. Blood culture became negative following myringotomy and drainage of an otitis media.

Numerous authors, notably Holmes and Randolph, have commented upon the fact that following pneumothorax "spreading involvement to new lobes is checked." It is of interest to note that in one patient (Case 3), even though treated on the first day of disease, a spread to the contralateral side occurred. In another patient (Case 1) a spread to an adjacent lobe took place while the latter was collapsed.

In this series massive pneumothorax therapy did not appear to induce strikingly beneficial results in the course of lobar pneumonia. Such a procedure is time-consuming, requires considerable technical skill, and is not without hazard. When carried to the point of producing and maintaining relatively complete collapse of the involved lung, the procedure becomes even more elaborate and its danger is not diminished. Although the maneuver relieves completely the initial pleural pain, it augments the symptoms of respiratory distress and may cause thoracic pain when intrapleural pressure is sufficiently

raised. A relatively small amount of air in the pleural cavity, on the other hand, relieves pleural pain and does not induce the other unpleasant symptoms. In spite of its objectionable features, massive pneumothorax would be of real value if it induced crisis, materially diminished the duration of the disease, or otherwise reduced the inherent dangers of lobar pneumonia, but in this series these desirable effects were not demonstrable.

SUMMARY

Final conclusions regarding the efficacy of pneumothorax therapy in lobar pneumonia can be reached only through very careful study of individual patients, since it is now obvious that favorable results can be obtained, if at all, only under certain particular conditions. The present report brings evidence bearing on the particular class of cases which may possibly be benefited and the special symptoms of the disease which may be relieved. The following conclusions may be drawn from the experience gained in the study of a series of cases treated in the Hospital of The Rockefeller Institute.

1. The introduction of large amounts of air into the pleural cavity with marked collapse of a pneumonic lung can be accomplished without serious harm to the patient.

2. Although massive pneumothorax is necessary to effect relatively complete collapse of the consolidated lung, it frequently causes an increase in dyspnea, tachypnea and cyanosis.

3. Pleural pain accompanying pneumonia is relieved after the introduction of a small amount of air into the pleural space, but larger amounts frequently induce substernal pain.

4. Certain changes in the systolic blood pressure following massive artificial pneumothorax appear to be related to the elevation of the intrapleural pressure.

5. Massive pneumothorax did not favorably influence the course of pneumonia in six early cases.

6. Decompression or withdrawal of air from the pleural cavity after subsidence of acute symptoms permitted re-expansion of the lung and did not cause reactivation of the infection.

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PLATE 1

FIG. 1. Case 1, 9 hours after onset of pneumococcus Type I pneumonia.

FIG. 2. Case 1, after 1550 cc. of air. (Pleural line retouched.)

FIG. 3. Case 1, after 3150 cc. of air, horizontal inspiration. (Expiration borders superimposed.)

FIG. 4. Case 1, after 3150 cc. of air, horizontal expiration. (Pleura retouched.)

FIG. 5. Case 1, after 3150 cc. of air, sitting inspiration.

FIG. 6. Case 1, after 3150 cc. of air, sitting expiration.

FIG. 7. Case 1, 6 days after onset, 12 hours after crisis—horizontal.

FIG. 8. Case 1, 6 days after onset, 12 hours after crisis—sitting.

FIG. 9. Case 1, after withdrawal of 2300 cc. of air—horizontal.

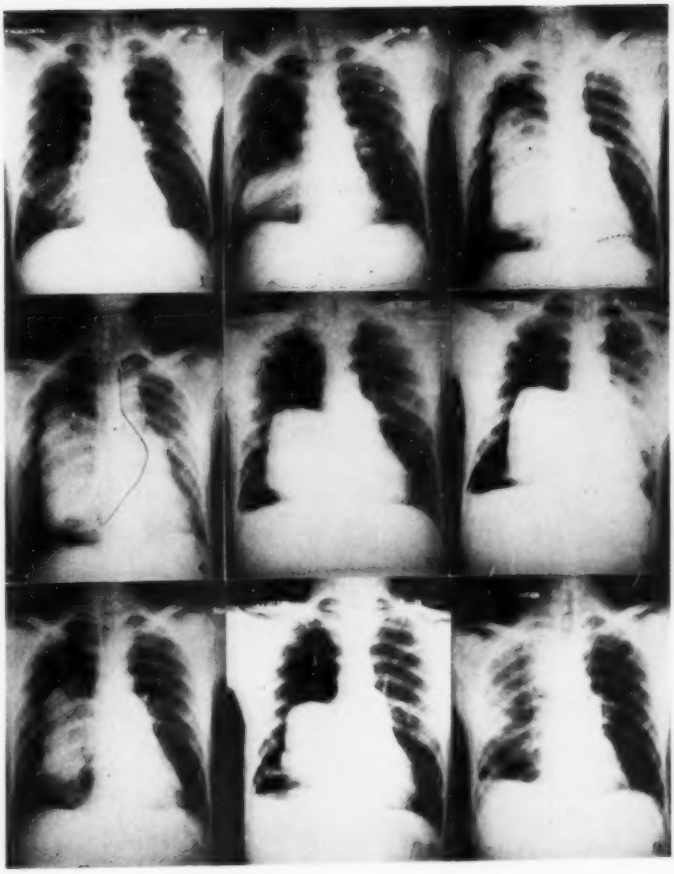

PLATE 2

FIG. 10. Case 1, after withdrawal of 2300 cc. of air—sitting.
FIG. 11. Case 1, 12 days after onset.
FIG. 12. Case 1, 25 days after onset.
FIG. 13. Case 2, 17 hours after onset of pneumococcus Type XIX pneumonia.
FIG. 14. Case 2, after 2000 cc. of air. (Pleura retouched.)
FIG. 15. Case 2, after 2600 cc. of air, horizontal inspiration.
FIG. 16. Case 2, after 2600 cc. of air, sitting inspiration.
FIG. 17. Case 2, 10 days after onset, sitting.
FIG. 18. Case 2, after withdrawal of 1000 cc. of air, sitting.

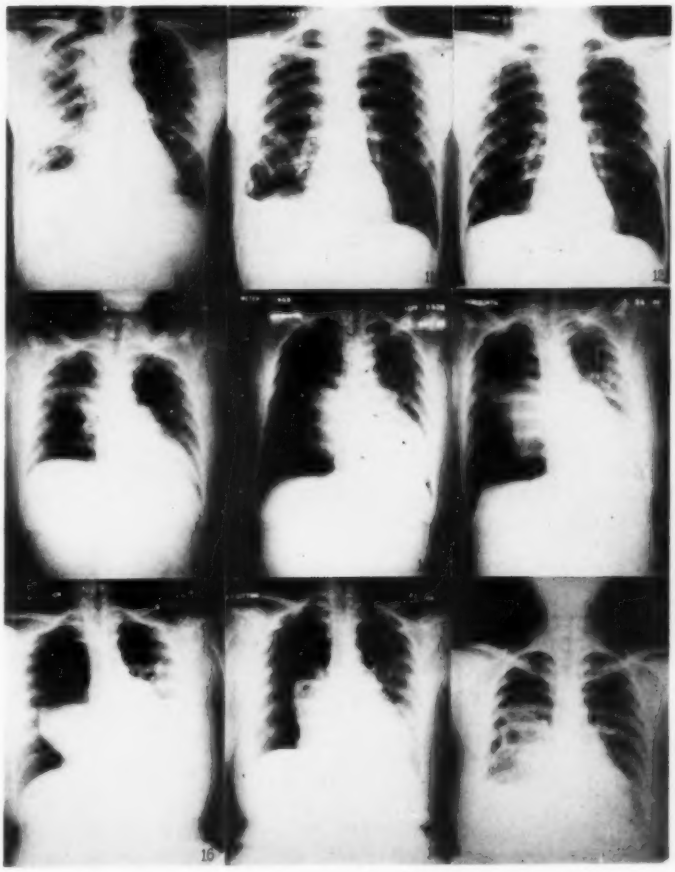

PLATE 3
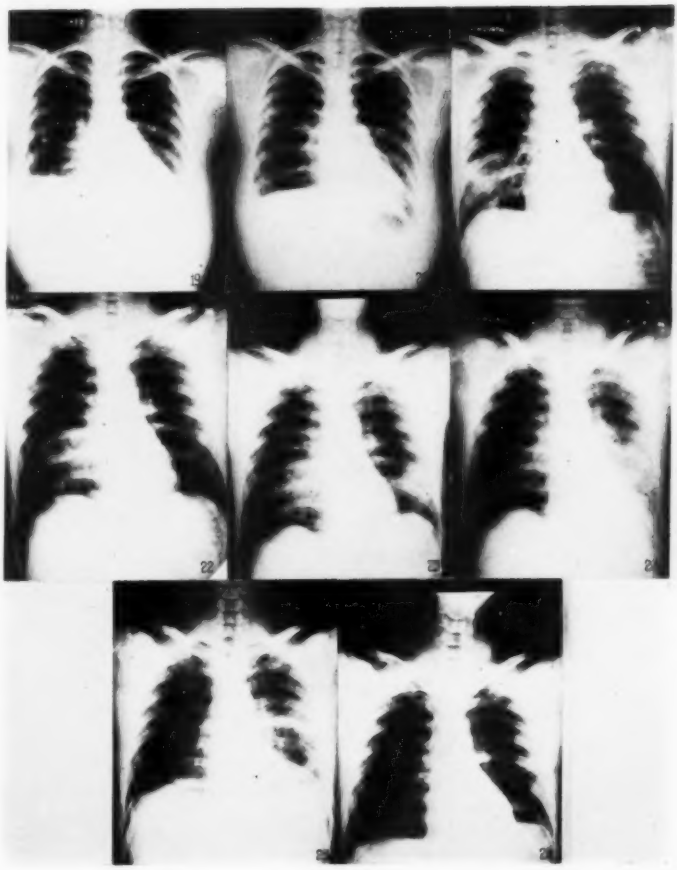
FIG. 19. Case 2, 14 days after onset.
FIG. 20. Case 2, 21 days after onset.
FIG. 21. Case 3, 16 hours after onset of pneumococcus Type VIII pneumonia.
FIG. 22. Case 3, after 2000 cc. of air. (Pleural line retouched.)
FIG. 23. Case 3, after 2500 cc. of air. (Pleural line retouched.) Note spread.
FIG. 24. Case 3, 3 days after onset. Note additional spread.
FIG. 25. Case 3, after withdrawal of 1300 cc. of air.
FIG. 26. Case 3, 14 days after onset.